



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C12N 15/12, C07K 14/705, C12N 15/62, C07K 16/28</b>		<b>A2</b>	(11) International Publication Number: <b>WO 99/63088</b> (43) International Publication Date: 9 December 1999 (09.12.99)																																																																		
(21) International Application Number: PCT/US99/12252 (22) International Filing Date: 2 June 1999 (02.06.99) (30) Priority Data: <table border="0"><tr><td>60/087,607</td><td>2 June 1998 (02.06.98)</td><td>US</td></tr><tr><td>60/087,609</td><td>2 June 1998 (02.06.98)</td><td>US</td></tr><tr><td>60/087,759</td><td>2 June 1998 (02.06.98)</td><td>US</td></tr><tr><td>60/087,827</td><td>3 June 1998 (03.06.98)</td><td>US</td></tr><tr><td>60/088,021</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,025</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,028</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,029</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,030</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,033</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,326</td><td>4 June 1998 (04.06.98)</td><td>US</td></tr><tr><td>60/088,167</td><td>5 June 1998 (05.06.98)</td><td>US</td></tr><tr><td>60/088,202</td><td>5 June 1998 (05.06.98)</td><td>US</td></tr><tr><td>60/088,212</td><td>5 June 1998 (05.06.98)</td><td>US</td></tr><tr><td>60/088,217</td><td>5 June 1998 (05.06.98)</td><td>US</td></tr><tr><td>60/088,655</td><td>9 June 1998 (09.06.98)</td><td>US</td></tr><tr><td>60/088,722</td><td>10 June 1998 (10.06.98)</td><td>US</td></tr><tr><td>60/088,730</td><td>10 June 1998 (10.06.98)</td><td>US</td></tr><tr><td>60/088,734</td><td>10 June 1998 (10.06.98)</td><td>US</td></tr><tr><td>60/088,738</td><td>10 June 1998 (10.06.98)</td><td>US</td></tr><tr><td>60/088,740</td><td>10 June 1998 (10.06.98)</td><td>US</td></tr><tr><td>60/088,741</td><td>10 June 1998 (10.06.98)</td><td>US</td></tr></table> <p style="text-align: center;">(Continued after the drawings)</p>			60/087,607	2 June 1998 (02.06.98)	US	60/087,609	2 June 1998 (02.06.98)	US	60/087,759	2 June 1998 (02.06.98)	US	60/087,827	3 June 1998 (03.06.98)	US	60/088,021	4 June 1998 (04.06.98)	US	60/088,025	4 June 1998 (04.06.98)	US	60/088,028	4 June 1998 (04.06.98)	US	60/088,029	4 June 1998 (04.06.98)	US	60/088,030	4 June 1998 (04.06.98)	US	60/088,033	4 June 1998 (04.06.98)	US	60/088,326	4 June 1998 (04.06.98)	US	60/088,167	5 June 1998 (05.06.98)	US	60/088,202	5 June 1998 (05.06.98)	US	60/088,212	5 June 1998 (05.06.98)	US	60/088,217	5 June 1998 (05.06.98)	US	60/088,655	9 June 1998 (09.06.98)	US	60/088,722	10 June 1998 (10.06.98)	US	60/088,730	10 June 1998 (10.06.98)	US	60/088,734	10 June 1998 (10.06.98)	US	60/088,738	10 June 1998 (10.06.98)	US	60/088,740	10 June 1998 (10.06.98)	US	60/088,741	10 June 1998 (10.06.98)	US	(71) Applicant (for all designated States except US): GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BAKER, Kevin [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). CHEN, Jian [CN/US]; 22-03 Hunters Glen Drive, Plainsboro, NJ 08536-3854 (US). GODDARD, Audrey [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). GURNEY, Austin, L. [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). SMITH, Victoria [AU/US]; 19 Dwight Road, Burlingame, CA 94010 (US). WATANABE, Colin, K. [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). WOOD, William, I. [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US). YUAN, Jean [CN/US]; 176 West 37th Avenue, San Mateo, CA 94403 (US). (74) Agents: KRESNAK, Mark, T. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
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(54) Title: MEMBRANE-BOUND PROTEINS AND NUCLEIC ACIDS ENCODING THE SAME																																																																					
(57) Abstract <p>The present invention is directed to polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.</p>																																																																					

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## NOVEL POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

### FIELD OF THE INVENTION

The present invention relates generally to the identification and isolation of novel DNA and to the recombinant production of novel polypeptides.

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### BACKGROUND OF THE INVENTION

Extracellular proteins play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

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Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci. 93:7108-7113 (1996); U.S. Patent No. 5,536,637)].

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Membrane-bound proteins and receptors can play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

1. **PRO281**

A novel gene designated testis enhanced gene transcript (TEGT) has recently been identified in humans (Walter et al., Genomics 20:301-304 (1995)). Recent results have shown that TEGT protein is developmentally regulated in the mammalian testis and possesses a nuclear targeting motif that allows the protein to localize to the nucleus (Walter et al., Mamm. Genome 5:216-221 (1994)). As such, it is believed that the TEGT protein plays an important role in testis development. There is, therefore, substantial interest in identifying and characterizing novel polypeptides having homology to the TEGT protein. We herein describe the identification and characterization of novel polypeptides having homology to TEGT protein, designated herein as PRO281 polypeptides.

2. **PRO276**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO276 polypeptides.

3. **PRO189**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO189 polypeptides.

4. **PRO190**

Of particular interest are proteins having seven transmembrane domains (7TM), or more generally, all multiple transmembrane spanning proteins. Among multiple transmembrane spanning proteins are ion channels and transporters. Examples of transporters are the UDP-galactose transporter described in Ishida, et al., J. Biochem., 120(6):1074-1078 (1996), and the CMP-sialic acid transporter described in Eckhardt, et al., PNAS, 93(15):7572-7576 (1996). We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO190 polypeptides.

**5. PRO341**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO341 polypeptides.

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**6. PRO180**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO180 polypeptides.

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**7. PRO194**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO194 polypeptides.

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**8. PRO203**

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. ATPases are a family of enzymes that play a variety of important roles, including energizing transport of ions and molecules, across cellular membranes. Transport mechanisms that employ ATPases often involve excluding xeno- and endobiotic toxins from the cellular environment, thereby protecting cells from toxicity of these compounds. Lu et al. report a detoxification mechanism where glutathione S-transferase (GST) catalyzes glutathionation of plant toxins, and a specific  $Mg^{2+}$ -ATPase is involved in the transport of the glutathione S-conjugates from the cytosol. Proc. Natl. Acad. Sci. USA 94(15):8243-8248 (1997). This study and others indicate the importance of the identification of ATPases, such as GST ATPases, and of novel proteins having sequence identity with ATPases.

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More generally, and also of interest are novel membrane-bound proteins, including those which may be involved in the transport of ions and molecules across membranes. Membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell

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interactions, and cellular adhesion molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

In light of the important physiological roles played by ATPases and membrane-bound proteins efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins, and proteins having sequence identity to ATPases. We herein describe the identification and characterization of novel polypeptides having sequence identity to GST ATPase, designated herein as PRO203 polypeptides.

#### 9. PRO290

Of particular interest are novel proteins and nucleic acids which have sequence identity with known proteins and nucleic acids. Proteins of interest which are well known in the art include NTII-1, a nerve protein which facilitates regeneration, FAN, and beige. Beige, or bg, is a murine analog related to Chediak-Higashi Syndrome (CHS), a rare autosomal recessive disease in which neutrophils, monocytes and lymphocytes contain giant cytoplasmic granules. See Perou et al., J. Biol. Chem. 272(47):29790 (1997) and Barbosa et al., Nature 382:262 (1996).

We herein describe the identification and characterization of novel polypeptides having sequence identity to NTII-1, FAN and beige, designated herein as PRO290 polypeptides.

#### 10. PRO874

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO194 polypeptides.

#### 11. PRO710

In *Saccharomyces cerevisiae*, the chromatin structure of DNA replication origins changes as cells become competent for DNA replication, suggesting that G1 phase-specific association of replication factors with origin DNA regulates entry into S phase (Aparicio et al., Cell 91:59-69 (1997)). In fact, it has been shown that the initiation of DNA replication in *Saccharomyces cerevisiae* requires the protein product of the CDC45 gene which encodes a protein that stays at relatively constant levels throughout the cell cycle (Owens et al., Proc. Natl. Acad. Sci USA 94:12521-12526 (1997)). The CDC45 protein is part of a prereplication complex that may move with DNA replication forks in yeast. Given the obvious importance of the CDC45 protein in DNA replication, there is significant interest in identifying and characterizing novel polypeptides having homology to CDC45. We herein describe the identification and characterization of novel polypeptides having homology to the CDC45 protein, designated herein as PRO710 polypeptides.



## 12. PRO1151

The complement proteins comprise a large group of serum proteins some of which act in an enzymatic cascade, producing effector molecules involved in inflammation. The complement proteins are of particular importance in regulating movement and function of cells involved in inflammation. One of the complement proteins, C1q, has been shown to be involved in the recognition of microbial surfaces and antibody-antigen complexes in the classical pathway of complement (Shapiro et al., Curr. Biol. 8(6):335-338 (1998)).

Given the physiological importance of inflammation and related mechanisms *in vivo* and in the specific physiological activities of complement C1q protein, efforts are currently being undertaken to identify new, native proteins which share sequence similarity to the complement proteins. We herein describe the identification and characterization of novel polypeptides having homology to complement C1q protein, designated herein as PRO1151 polypeptides.

## 13. PRO1282

All proteins containing leucine-rich repeats are thought to be involved in protein-protein interactions. Leucine-rich repeats are short sequence motifs present in a number of proteins with diverse functions and cellular locations. The crystal structure of ribonuclease inhibitor protein has revealed that leucine-rich repeats correspond to beta-alpha structural units. These units are arranged so that they form a parallel beta-sheet with one surface exposed to solvent, so that the protein acquires an unusual, nonglobular shape. These two features have been indicated as responsible for the protein-binding functions of proteins containing leucine-rich repeats. See, Kobe and Deisenhofer, Trends Biochem. Sci., 19(10):415-421 (Oct. 1994); Kobe and Deisenhofer, Curr. Opin. Struct. Biol., 5(3):409-416 (1995).

A study has been reported on leucine-rich proteoglycans which serve as tissue organizers, orienting and ordering collagen fibrils during ontogeny and are involved in pathological processes such as wound healing, tissue repair, and tumor stroma formation. Iozzo, R. V., Crit. Rev. Biochem. Mol. Biol., 32(2):141-174 (1997). Others studies implicating leucine rich proteins in wound healing and tissue repair are De La Salle, C., et al., Vouv. Rev. Fr. Hematol. (Germany), 37(4):215-222 (1995), reporting mutations in the leucine rich motif in a complex associated with the bleeding disorder Bernard-Soulier syndrome, Chlemetson, K. J., Thromb. Haemost. (Germany), 74(1):111-116 (July 1995), reporting that platelets have leucine rich repeats and Ruoslahti, E. I., et al., WO9110727-A by La Jolla Cancer Research Foundation reporting that decorin binding to transforming growth factor $\beta$  has involvement in a treatment for cancer, wound healing and scarring. Related by function to this group of proteins is the insulin like growth factor (IGF), in that it is useful in wound-healing and associated therapies concerned with re-growth of tissue, such as connective tissue, skin and bone; in promoting body growth in humans and animals; and in stimulating other growth-related processes. The acid labile subunit of IGF (ALS) is also of interest in that it increases the half-life of IGF and is part of the IGF complex *in vivo*.

Another protein which has been reported to have leucine-rich repeats is the SLIT protein which has been reported to be useful in treating neuro-degenerative diseases such as Alzheimer's disease, nerve damage such as in Parkinson's disease, and for diagnosis of cancer, see, Artavanistsakonas, S. and Rothberg, J. M., WO9210518-A1 by Yale University. Of particular interest is LIG-1, a membrane glycoprotein that is expressed

specifically in glial cells in the mouse brain, and has leucine rich repeats and immunoglobulin-like domains. Suzuki, et al., J. Biol. Chem. (U.S.), 271(37):22522 (1996). Other studies reporting on the biological functions of proteins having leucine rich repeats include: Tayar, N., et al., Mol. Cell Endocrinol., (Ireland), 125(1-2):65-70 (Dec. 1996) (gonadotropin receptor involvement); Miura, Y., et al., Nippon Rinsho (Japan), 54(7):1784-1789 (July 1996) (apoptosis involvement); Harris, P. C., et al., J. Am. Soc. Nephrol., 6(4):1125-1133 (Oct. 1995) (kidney disease involvement).

Leucine rich repeat proteins are further discussed in Kajava, J. Mol. Biol., 277(3):519-527 (1998), Nagasawa, et al., Genomics, 44(3):273-279 (1997), Bengtsson, J. Biol. Chem., 270(43):25639-25644 (1995), Gaillard, et al., Cell, 65(7):1127-1141 (1991) and Ohkura and Yanagida, Cell, 64(1):149-157 (1991), all incorporated herein by reference.

Thus, due to all the reasons listed above, new members of the leucine rich repeat superfamily are of interest. On a more general level, all novel proteins are of interest. We herein describe the identification and characterization of novel leucine-rich repeat-containing polypeptides, designated herein as PRO1282 polypeptides.

#### 14. PRO358

The cloning of the Toll gene of *Drosophila*, a maternal effect gene that plays a central role in the establishment of the embryonic dorsal-ventral pattern, has been reported by Hashimoto et al., Cell 52:269-279 (1988). The *Drosophila* Toll gene encodes an integral membrane protein with an extracytoplasmic domain of 803 amino acids and a cytoplasmic domain of 269 amino acids. The extracytoplasmic domain has a potential membrane-spanning segment, and contains multiple copies of a leucine-rich segment, a structural motif found in many transmembrane proteins. The Toll protein controls dorsal-ventral patterning in *Drosophila* embryos and activates the transcription factor Dorsal upon binding to its ligand Spätzle. (Morisato and Anderson, Cell 76:677-688 (1994)). In adult *Drosophila*, the Toll/Dorsal signaling pathway participates in the anti-fungal immune response. (Lenaitre et al., Cell 86:973-983 (1996)).

A human homologue of the *Drosophila* Toll protein has been described by Medzhitov et al., Nature 388:394-397 (1997). This human Toll, just as *Drosophila* Toll, is a type I transmembrane protein, with an extracellular domain consisting of 21 tandemly repeated leucine-rich motifs (leucine-rich region - LRR), separated by a non-LRR region, and a cytoplasmic domain homologous to the cytoplasmic domain of the human interleukin-1 (IL-1) receptor. A constitutively active mutant of the human Toll transfected into human cell lines was shown to be able to induce the activation of NF- $\kappa$ B and the expression of NF- $\kappa$ B-controlled genes for the inflammatory cytokines IL-1, IL-6 and IL-8, as well as the expression of the costimulatory molecule B7.1, which is required for the activation of native T cells. It has been suggested that Toll functions in vertebrates as a non-clonal receptor of the immune system, which can induce signals for activating both an innate and an adaptive immune response in vertebrates. The human Toll gene reported by Medzhitov et al., *supra* was most strongly expressed in spleen and peripheral blood leukocytes (PBL), and the authors suggested that its expression in other tissues may be due to the presence of macrophages and dendritic cells, in which it could act as an early-warning system for infection. The public GenBank database contains the following Toll sequences: Toll1



(DNAX# HSU88540-1, which is identical with the random sequenced full-length cDNA #HUMRSC786-1); Toll2 (DNAX# HSU88878-1); Toll3 (DNAX# HSU88879-1); and Toll4 (DNAX# HSU88880-1, which is identical with the DNA sequence reported by Medzhitov et al., *supra*). A partial Toll sequence (Toll5) is available from GenBank under DNAX# HSU88881-1.

Further human homologues of the *Drosophila* Toll protein, designated as Toll-like receptors (huTLRs 1-5) were recently cloned and shown to mirror the topographic structure of the *Drosophila* counterpart (Rock et al., *Proc. Natl. Acad. Sci. USA* 95:588-593 [1998]). Overexpression of a constitutively active mutant of one human TLR (Toll-protein homologue - Medzhitov et al., *supra*; TLR4 - Rock et al., *supra*) leads to the activation of NF- $\kappa$ B and induction of the inflammatory cytokines and constimulatory molecules. Medzhitov et al., *supra*.

We herein describe the identification and characterization of novel polypeptides having homology to Toll, designated herein as PRO358 polypeptides.

#### 15. PRO1310

Of interest are proteins related to carboxypeptidases. Various carboxypeptidases are described in the literature, i.e., Krause et al., *Immunol. Rev.* 161:119-127 (1998) and Leiter, *J. Endocrinol.* 155(2):211-214 (1997). We herein describe the identification and characterization of novel polypeptides having homology to a carboxypeptidase, designated herein as PRO1310 polypeptides.

#### 16. PRO698

The extracellular mucous matrix of olfactory neuroepithelium is a highly organized structure in intimate contact with chemosensory cilia that house the olfactory transduction machinery. The major protein component of this extracellular matrix is olfactomedin, a glycoprotein that is expressed in olfactory neuroepithelium and which form intermolecular disulfide bonds so as to produce a polymer (Yokoe et al., *Proc. Natl. Acad. Sci. USA* 90:4655-4659 (1993), Bal et al., *Biochemistry* 32:1047-1053 (1993) and Snyder et al., *Biochemistry* 30:9143-9153 (1991)). It has been suggested that olfactomedin may influence the maintenance, growth or differentiation of chemosensory cilia on the apical dendrites of olfactory neurons. Given this important role, there is significant interest in identifying and characterizing novel polypeptides having homology to olfactomedin. We herein describe the identification and characterization of novel polypeptides having homology to olfactomedin protein, designated herein as PRO698 polypeptides.

#### 17. PRO732

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides having sequence identity to the Diff33 protein, designated herein as PRO732 polypeptides.

**18. PRO1120**

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Sulfatases are a family of secreted enzymatic proteins that play a variety of important metabolic roles and thus are the subject of interest in research and industry (see, e.g., Sleat et al., Biochem J., 324(Pt. 1):33-39 (1997)). Deficiencies of certain sulfatases have been implicated in various human disorders including Sanfilippo D syndrome (see, Litjens et al., Biochem J. 327(Pt 1):899-94 (1997); Leipprandt et al. J. Inherit Metab. Dis. 18(5):647-648 (1995); and Freeman et al. Biochem J. 282(pt2):605-614 (1992)). We herein describe the identification and characterization of novel polypeptides having sequence identity to sulfatase protein, designated herein as PRO1120 polypeptides.

**19. PRO537**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO537 polypeptides.

**20. PRO536**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO536 polypeptides.

**21. PRO535**

Isomerase proteins play many important physiological roles in the mammal. Many different types of isomerase proteins have been identified and characterized including, for example, protein disulfide isomerases and peptidyl-prolyl isomerases. It has been reported that many immunophilin proteins, i.e., proteins that serves as receptors for immunosuppressant drugs, exhibit peptidyl-prolyl isomerase activity in that they function to catalyze the interconversion of the cis and trans isomerase of peptide and protein substrates for immunophilin proteins. As such, there is significant interest in identifying and characterizing novel polypeptides having sequence similarity to peptidyl-prolyl isomerase proteins. We herein describe the identification and characterization of novel polypeptides having homology to a putative peptidyl-prolyl isomerase protein, designated herein as PRO535 polypeptides.

**22. PRO718**

Efforts are being undertaken by both industry and academia to identify new, native transmembrane proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel transmembrane proteins. We herein describe the identification and

characterization of novel transmembrane polypeptides, designated herein as PRO718 polypeptides.

23. **PRO872**

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Dehydrogenases and desaturases are a family of enzymes that play a variety of important metabolic roles and thus are the subject of interest in research and industry (see Hable et al., Mol. Gen. Genet. 257(2):167-176 (1998); Schneider, C. et al., Prot. Expr. Purif. 10(2):175-179 (1997)). We herein describe the identification and characterization of novel polypeptides having sequence identity to dehydrogenase proteins, designated herein as PRO872 polypeptides.

24. **PRO1063**

Collagens constitute the most abundant proteins of the extracellular matrix (ECM) in mammalian organisms. Collagen and other macromolecules of the ECM are deposited by resident cells and organized into a three-dimensional meshwork. This ECM environment plays an essential role in guiding cell migration and in cell-to-cell communication during morphogenic processes. The restructuring of the ECM during remodeling occurs as a cooperative multistep process involving a localized degradation of existing macromolecules, rearrangement of the cytoskeleton, cell translocation, and deposition of new ECM components. Involved in this restructuring are enzymes such as collagenases and gelatinases which play important roles in the degradation of the ECM. In light of the obviously important roles played by the collagenase enzymes, there is substantial interest in identifying and characterizing novel polypeptides having homology to these proteins. We herein describe the identification and characterization of novel polypeptides having homology to human type IV collagenase protein, designated herein as PRO1063 polypeptides.

25. **PRO619**

Immunoglobulins are antibody molecules, the proteins that function both as receptors for antigen on the B-cell membrane and as the secreted products of the plasma cell. Like all antibody molecules, immunoglobulins perform two major functions: they bind specifically to an antigen and they participate in a limited number of biological effector functions. Therefore, new members of the Ig superfamily are always of interest.

Of particular interest are novel gene products associated with mu chains in immature B cells. Shirasawa, et al., EMBO J., 12(5):1827-1834 (1993); Dul, et al., Eur. J. Immunol., 26(4):906-913 (1996). Moreover, the molecular components and assembly of mu surrogate light chain complexes in pre-B cell lines are of interest. Ohnishi and Takemori, J. Biol. Chem., 269(45):28347-28353 (1994); Bauer, et al., Curr. Top. Microbiol., 137:130-135 (1988). Novel nucleic acids and peptides related to VpreB1, VpreB2 and VpreB3 by sequence identity are of particular interest. The assembly and manipulation of immunoglobulins can effect the entire industry related to antibodies and vaccines.

We herein describe the identification and characterization of novel polypeptides having homology to VpreB proteins, designated herein as PRO619 polypeptides.

**26.     PRO943**

Fibroblast growth factor (FGF) proteins exhibit a variety of activities and act by binding to cell surface fibroblast growth factor receptors. Many different fibroblast growth factor receptors have been identified and characterized, including the fibroblast growth factor receptor-4, which has been shown to be a high affinity receptor for both acidic and basic FGF (Ron et al., J. Biol. Chem. 268:5388-5394 (1993) and Stark et al., Development 113:641-651 (1991)). Given the obvious importance of the FGF family of proteins and the cell surface receptors to which they bind, there is significant interest in identifying novel polypeptides having homology to the FGF receptor family. We herein describe the identification and characterization of novel polypeptides having homology to the fibroblast growth factor receptor-4 protein, designated herein as PRO943 polypeptides.

**27.     PRO1188**

The identification of nucleotide pyrophosphohydrolases has been of interest because of the potential roles these secreted molecules play in calcium pyrophosphate dihydrate (CPPD) deposition disease, arthritis, and other joint diseases (see Masuda et al. J. Rheumatol. (1997) 24(8):1588-1594; and Terkeltaub et al., Arthritis Rheum (1998) 37(6):934-941). We herein describe the identification and characterization of novel polypeptides having homology to nucleotide pyrophosphohydrolases, designated herein as PRO1188 polypeptides.

**28.     PRO1133**

Netrins are molecules that guide growing axons and that are strikingly similar in sequence and in function in flies, nematodes and vertebrates. Additionally, netrin receptors have been identified in all three animal groups and shown to have crucial, conserved roles in axon navigation. Netrins and their receptors are further described in the literature, i.e., Varela-Echavarria and Guthrie, Genes Dev., 11(5):545-557 (1997); Guthrie, Curr. Biol., 7(1):R6-R9 (1997); and Keynes and Cook, Neuron, 17(6):1031-1034 (1996). Due to their relation to neurons, netrins and their related proteins are of interest. Of particular interest are molecules having sequence identity or similarity with netrin. We herein describe the identification and characterization of novel polypeptides having homology to netrins, designated herein as PRO1133 polypeptides.

**29.     PRO784**

Of interest are membrane-bound and receptor proteins involved in intracellular signaling, metabolism, transport, and other pathways. For example, membrane-bound proteins of the endoplasmic reticulum and golgi apparatus play important roles in the transport of proteins. The sec22 protein is an endoplasmic reticulum membrane-bound protein involved in fundamental membrane trafficking reactions where secretory products are routed from their site of synthesis to their final destination. The roles of sec22 in transport pathways have been reported by numerous investigators (see Tang et al., Biochem Biophys Res Commun 243(3):885-891 (1998); Hay et al., J. Biol. Chem. 271(10):5671-5679 (1996); and Newman et al., Mol. Cell. Biol. 10(7):3405-3414 (1990)). We herein describe the identification and characterization of novel polypeptides having homology to sec22, designated herein as PRO784 polypeptides.



**30.     PRO783**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO783 polypeptides.

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**31.     PRO820**

Immunoglobulin molecules play roles in many important mammalian physiological processes. The structure of immunoglobulin molecules has been extensively studied and it has been well documented that intact immunoglobulins possess distinct domains, one of which is the constant domain or F<sub>c</sub> region of the immunoglobulin molecule. The F<sub>c</sub> domain of an immunoglobulin, while not being directly involved in antigen recognition and binding, does mediate the ability of the immunoglobulin molecule, either uncomplexed or complexed with its respective antigen, to bind to F<sub>c</sub> receptors either circulating in the serum or on the surface of cells. The ability of an F<sub>c</sub> domain of an immunoglobulin to bind to an F<sub>c</sub> receptor molecule results in a variety of important activities, including for example, in mounting an immune response against unwanted foreign particles. Thus, molecules related to F<sub>c</sub> receptors are of interest. F<sub>c</sub> receptors are further described in Tominaga et al., Biochem. Biophys. Res. Commun., 168(2):683-689 (1990); Zhang et al., Immuno., 39(6):423-427 (1994). We herein describe the identification and characterization of novel polypeptides having homology to F<sub>c</sub> receptor, designated herein as PRO820 polypeptides.

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**20    32.     PRO1080**

The folding of proteins and the assembly of protein complexes within subcompartments of the eukaryotic cell is catalysed by different members of the Hsp70 protein family. The chaperone function of Hsp70 proteins in these events is regulated by members of the DnaJ-like protein family, which occurs through direct interaction of different Hsp70 and DnaJ-like protein pairs that appear to be specifically adapted to each other. The diversity of functions of DnaJ-like proteins using specific examples of DnaJ-Hsp70 interactions with polypeptides in yeast protein-biogenesis pathways is further described in Cyr et al., Trends Biochem. Sci., 19(4):176-181 (1994). DnaJ proteins and their involvement in the binding of secretory precursor polypeptides to a translocon subcomplex and polypeptide translocation machinery in the yeast endoplasmic reticulum are further described in Lyman and Schekman, Cell 88(1):85-96 (1997) and Lyman and Schekman, Experientia 52(12):1042-1049 (1996), respectively. Thus, DnaJ proteins are of interest, as are proteins related to DnaJ proteins, particularly those having sequence identity with DnaJ proteins. We herein describe the identification and characterization of novel polypeptides having homology to DnaJ proteins, designated herein as PRO1080 polypeptides.

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**33.     PRO1079**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel

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secreted polypeptides, designated herein as PRO1079 polypeptides.

34. **PRO793**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to  
5 identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO793 polypeptides.

35. **PRO1016**

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods,  
10 the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Acyltransferases are enzymes which acylate moieties. Acyl-glycerol-phosphate acyltransferases can act on lysophosphatidic acid as a substrate. The lysophosphatidic acid is converted to phosphatidic acid and thus plays a role in forming phosphatidylethanolamine found in membranes. See, Brown, et al., Plant Mol. Biol., 26(1):211-223 (1994). Thus, acyltransferases play an important role in the biosynthesis  
15 of molecules requiring acylation. We herein describe the identification and characterization of novel polypeptides having homology to acyltransferase proteins, designated herein as PRO1016 polypeptides.

36. **PRO1013**

Efforts are being undertaken by both industry and academia to identify new, native proteins. Many of  
20 these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel proteins. We herein describe the identification and characterization of novel polypeptides, designated herein as PRO1013 polypeptides.

37. **PRO937**

The glypican family of heparan sulfate proteoglycans are major cell-surface proteoglycans of the  
25 developing nervous system. It is believed that members of the glypican family play a role in regulating cell cycle progression during the transition of proliferating neuronal progenitor cells to differentiated neurons. Lander et al. Perspect Dev. Neurobiol 3(4):347-358 (1996). It is likely that proteoglycans of the glypican family play other important roles in neural development (Lander et al., *supra*), and as well as other tissues, as glypican family  
30 members have also been found in the developing kidney (Watanabe et al. J. Cell Biol. 130(5):1207-1218 (1995)). Accordingly, the identification of new members of the glypican family of proteins is of interest in research and in industry.

Described herein is the identification and characterization of novel polypeptides having sequence identity with glypican family proteins, designated herein as PRO937 polypeptides.

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**38. PRO842**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO842 polypeptides.

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**39. PRO839**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO839 polypeptides.

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**40. PRO1180**

Methyltransferase enzymes catalyze the transfer of methyl groups from a donor molecule to an acceptor molecule. Methyltransferase enzymes play extremely important roles in a number of different biological processes including, for example, in the electron transport chain in the plasma membrane in prokaryotes and in the inner mitochondrial membrane in eukaryotic cells (see, e.g., Barkovich et al., *J. Biol. Chem.* 272:9182-9188 (1997), Dibrov et al., *J. Biol. Chem.* 272:9175-9181 (1997), Lee et al., *J. Bacteriol.* 179:1748-1754 (1997) and Marbois et al., *Arch. Biochem. Biophys.* 313:83-88 (1994)). Methyltransferase enzymes have been shown to be essential for the biosynthesis of ubiquinone (coenzyme Q) and menaquinone (vitamin K2), both of which are essential isoprenoid quinone components of the respiratory electron transport chain. Given the obvious importance of the methyltransferase enzymes, there is substantial interest in identifying novel polypeptide homologs of the methyltransferases. We herein describe the identification and characterization of a novel polypeptide having homology to methyltransferase enzymes, designated herein as PRO1180 polypeptides..

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**41. PRO1134**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1134 polypeptides.

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**42. PRO830**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO830 polypeptides.

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43. **PRO1115**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1115 polypeptides.

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44. **PRO1277**

Efforts are being undertaken by both industry and academia to identify new, native proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor and other proteins. Of interest is the identification of proteins that may play roles in various human disorders and dysfunction. For example, the identification of proteins of the ear and the functions they play in hearing may lead to an understanding of the causes of hearing loss and deafness. Coch-B2 is one such protein that has been found to be specifically expressed in the inner ear (cochlea). It has been characterized and studied for its possible role in hearing loss (Robertson et al. Genomics (1994) 23(1):52-50; Robertson et al. Genomics (1997) 46(3):345-354). We herein describe the identification and characterization of novel polypeptides having sequence identity to Coch-B2, designated herein as PRO1277 polypeptides.

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45. **PRO1135**

Glycosylation is an important mechanism for modulating the physiochemical and biological properties of proteins in a stage- and tissue-specific manner. One of the important enzymes involved in glycosylation in *Saccharomyces cerevisiae* is alpha 1,2-mannosidase, an enzyme that catalyzes the conversion of Man9GlcNAc2 to Man8GlcNAc2 during the formation of N-linked oligosaccharides. The *Saccharomyces cerevisiae* alpha 1,2-mannosidase enzyme is a member of the Class I alpha 1,2-mannosidases that are conserved from yeast to mammals. Given the important roles played by the alpha 1,2-mannosidases in glycosylation and the physiochemical activity regulated by glycosylation, there is significant interest in identifying novel polypeptides having homology to one or more mannosidases. We herein describe the identification and characterization of novel polypeptides having homology to alpha 1,2-mannosidase protein, designated herein as PRO1135 polypeptides.

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46. **PRO1114**

Interferons (IFNs) encompass a large family of secreted proteins occurring in vertebrates. Although they were originally named for their antiviral activity, growing evidence supports a critical role for IFNs in cell growth and differentiation (Jaramillo et al., Cancer Investigation 13(3):327-338 (1995)). IFNs belong to a class of negative growth factors having the ability to inhibit the growth of a wide variety of cells with both normal and transformed phenotypes. IFN therapy has been shown to be beneficial in the treatment of human malignancies such as Kaposi's sarcoma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and hairy cell leukemia as well as in the treatment of infectious diseases such as hepatitis B (Gamliel et al., Scanning Microscopy 2(1):485-492 (1988), Einhorn et al., Med. Oncol. & Tumor Pharmacother. 10:25-29 (1993), Ringenberg et al.,

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Missouri Medicine 85(1):21-26 (1988), Saracco et al., Journal of Gastroenterology and Hepatology 10:668-673 (1995), Gonzalez-Mateos et al., Hepato-Gastroenterology 42:893-899 (1995) and Malaguarnera et al., Pharmacotherapy 17(5):998-1005 (1997)).

Interferons can be classified into two major groups based upon their primary sequence. Type I interferons, IFN- $\alpha$  and IFN- $\beta$ , are encoded by a superfamily of intronless genes consisting of the IFN- $\alpha$  gene family and a single IFN- $\beta$  gene that are thought to have arisen from a common ancestral gene. Type I interferons may be produced by most cell types. Type II IFN, or IFN- $\gamma$ , is restricted to lymphocytes (T cells and natural killer cells) and is stimulated by nonspecific T cell activators or specific antigens *in vivo*.

Although both type I and type II IFNs produce similar antiviral and antiproliferative effects, they act on distinct cell surface receptors, wherein the binding is generally species specific (Langer et al., Immunol. Today 9:393-400 (1988)). Both IFN- $\alpha$  and IFN- $\beta$  bind competitively to the same high affinity type I receptor, whereas IFN- $\gamma$  binds to a distinct type II receptor. The presence and number of IFN receptors on the surface of a cell does not generally reflect the sensitivity of the cell to IFN, although it is clear that the effects of the IFN protein is mediated through binding to a cell surface interferon receptor. As such, the identification and characterization of novel interferon receptor proteins is of extreme interest.

We herein describe the identification and characterization of novel interferon receptor polypeptides, designated herein as "PRO1114 interferon receptor" polypeptides. Thus, the PRO1114 polypeptides of the present invention represents a novel cell surface interferon receptor.

#### 47. PRO828

Glutathione peroxidases are of interest because they play important roles in protection against risk of coronary disease, atherosclerosis, platelet hyperaggregation and synthesis of proaggregant and proinflammatory compounds. Glutathione peroxidases are involved in the reduction of hydrogen peroxides and lipid peroxides, which in turn regulate the activities of cyclooxygenase and lipooxygenase pathways. This ultimately influences the production of eicosanoids and modulates the balance between a proaggregatory and antiaggregatory state of platelets. These and other activities and functions of glutathione peroxidases are discussed in greater detail by Ursini et al., Biomed. Environ. Sci 10(2-3): 327-332 (1997); Vitoux et al., Ann. Biol. Clin (Paris) 54(5): 181-187 (1996); and Mirault et al., Ann N.Y. Acad. Sci 738: 104-115 (1994).

We herein describe the identification and characterization of novel polypeptides having sequence identity with glutathione peroxidases, designated herein as PRO828 polypeptides.

#### 48. PRO1009

Long chain acyl-CoA synthetase converts free fatty acids to acyl-CoA esters. This synthetase has been reported to have interesting characteristics. Specifically, it has been reported that two boys having Alport syndrome, elliptocytosis and mental retardation carried a large deletion where long chain acyl-CoA synthetase 4 would have been located. Thus, the absence of this enzyme is believed to play a role in the development of mental retardation or other signs associated with Alport syndrome in the family. Piccini, et al., Genomics, 47(3):350-358 (1998). Moreover, it has been reported that an inhibitor of acyl coenzyme A synthetase, triacsin

C, inhibits superoxide anion generation and degranulation by human neutrophils. Thus, it is suggested that there is a role for acyl-CoA esters in regulating activation of  $O_2$  generation and degranulation at the G protein or subsequent step(s). Korchak, et al., *J. Biol. Chem.*, 269(48):30281-30287 (1994). Long chain acyl-CoA synthetase is also briefly discussed in a report which describes very long chain acyl-CoA synthetase. Uchiyama, et al., *J. Biol. Chem.*, 271(48):30360 (1994). Thus, long chain acyl-CoA synthetase and particular novel polypeptides having sequence identity therewith are of interest.

We herein describe the identification and characterization of novel polypeptides having sequence identity with long chain acyl-CoA synthetase, designated herein as PRO1009 polypeptides.

#### 49. PRO1007

Glycosylphosphatidylinositol (GPI) anchored proteoglycans are generally localized to the cell surface and are thus known to be involved in the regulation of responses of cells to numerous growth factors, cell adhesion molecules and extracellular matrix components. The metastasis-associated GPI-anchored protein (MAGPIAP) is one of these cell surface proteins which appears to be involved in metastasis. Metastasis is the form of cancer wherein the transformed or malignant cells are traveling and spreading the cancer from one site to another. Therefore, identifying the polypeptides related to metastasis and MAGPIAP is of interest.

We herein describe the identification and characterization of novel polypeptides having sequence identity with MAGPIAP, designated herein as PRO1007 polypeptides.

#### 50. PRO1056

Mammalian cell membranes perform very important functions relating to the structural integrity and activity of various cells and tissues. Of particular interest in membrane physiology is the study of trans-membrane ion channels which act to directly control a variety of physiological, pharmacological and cellular processes. Numerous ion channels have been identified including calcium (Ca), sodium (Na), chloride (Cl) and potassium (K) channels, each of which have been analyzed in detail to determine their roles in physiological processes in vertebrate and insect cells. These roles include such things as maintaining cellular homeostasis, intracellular signaling, and the like. Given the obvious importance of the ion channels, there is significant interest in identifying and characterizing novel polypeptides having homology to one or more ion channels. We herein describe the identification and characterization of novel polypeptides having homology to a chloride channel protein, designated herein as PRO1056 polypeptides..

#### 51. PRO826

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO826 polypeptides.



**52. PRO819**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO819 polypeptides.

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**53. PRO1006**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1006 polypeptides.

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**54. PRO1112**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1112 polypeptides.

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**55. PRO1074**

Many membrane-bound enzymatic proteins play important roles in the chemical reactions involved in metabolism, including the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, development of tissues, and other processes necessary to sustain life. Galactosyltransferases are a family of enzymes that play a variety of important metabolic roles and thus are the subject of interest in research and industry. Numerous references have been published on the identification of galactosyltransferases and the roles they play in cellular development, maintenance, and dysfunction.

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We herein describe the identification and characterization of novel polypeptides having homology to galactosyltransferases, designated herein as PRO1074 polypeptides.

**56. PRO1005**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1005 polypeptides.

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**57. PRO1073**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel

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secreted polypeptides, designated herein as PRO1073 polypeptides.

58. **PRO1152**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to  
5 identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1152 polypeptides.

59. **PRO1136**

PDZ domain-containing proteins assist formation of cell-cell junctions and localization of membrane  
10 protein receptors and ion channels (Daniels et al., Nat. Struct. Biol. 5:317-325 (1998) and Ullmer et al., FEBS Lett. 424:63-68 (1998)). PDZ domains interact with the C-terminal residues of a particular target membrane protein. Based on their binding specificities and sequence homologies, PDZ domains fall into two classes, class I and class II. In light of the obvious importance of the PDZ domain-containing proteins, there is significant interest in identifying novel polypeptides that have homology to those proteins. We herein describe the  
15 identification and characterization of novel polypeptides having homology to PDZ domain-containing proteins, designated herein as PRO1136 polypeptides.

60. **PRO813**

Surfactant proteins play extremely important biological roles in the mammalian pulmonary system. One  
20 mammalian protein that has been studied and well characterized is pulmonary surfactant-associated protein C. For example, Qanbar et al., Am. J. Physiol. 271:L572-L580 (1996) studied the effect of palmitoylation of pulmonary surfactant-associated protein C on the surface activity of phospholipid mixtures. Specifically, the authors demonstrated that palmitoylation of pulmonary surfactant-associated protein C greatly enhanced lipid respreading and film stability and, therefore, was extremely important for surfactant function. Given the obvious  
25 important roles played by surfactant protein in the mammalian organism, there is significant interest in identifying novel polypeptides having homology to one or more surfactant enzymes. We herein describe the identification and characterization of novel polypeptides having homology to pulmonary surfactant-associated protein, designated herein as PRO813 polypeptides.

30 61. **PRO809**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO809 polypeptides.

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**62. PRO791**

Of particular interest are novel proteins which have sequence identity with known proteins. For example, novel proteins having some sequence identity with the major histocompatibility complex (MHC) are of interest. The MHC complex is a region of multiple loci that play major roles in determining whether transplanted tissue will be accepted as self (histocompatible) or rejected as foreign (histoincompatible).

Moreover, the MHC plays a central role in the development of both humoral and cell-mediated immune responses. There are class I, II and III MHC antigens, all known in the art. Class I antigens are glycoproteins expressed on the surface of nearly all nucleated cells, where they present peptide antigens of altered self-cells necessary for the activation of Tc cells. The assembly of MHC class I antigens is further described in Kvist and Levy, Semin. Immunol., 5(2):105-116 (1993) and Maffei, et al., Hum. Immunol., 54(2):91-103 (1997).

We herein describe the identification and characterization of novel polypeptides having sequence identity to various MHC-I antigens, designated herein as PRO791 polypeptides.

**63. PRO1004**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins.

Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1004 polypeptides.

**64. PRO1111**

Protein-protein interactions include receptor and antigen complexes and signaling mechanisms. As more is known about the structural and functional mechanisms underlying protein-protein interactions, protein-protein interactions can be more easily manipulated to regulate the particular result of the protein-protein interaction. Thus, the underlying mechanisms of protein-protein interactions are of interest to the scientific and medical community.

All proteins containing leucine-rich repeats are thought to be involved in protein-protein interactions. Leucine-rich repeats are short sequence motifs present in a number of proteins with diverse functions and cellular locations. The crystal structure of ribonuclease inhibitor protein has revealed that leucine-rich repeats correspond to beta-alpha structural units. These units are arranged so that they form a parallel beta-sheet with one surface exposed to solvent, so that the protein acquires an unusual, nonglobular shape. These two features have been indicated as responsible for the protein-binding functions of proteins containing leucine-rich repeats. See, Kobe and Deisenhofer, Trends Biochem. Sci., 19(10):415-421 (Oct. 1994).

A study has been reported on leucine-rich proteoglycans which serve as tissue organizers, orienting and ordering collagen fibrils during ontogeny and are involved in pathological processes such as wound healing, tissue repair, and tumor stroma formation. Iozzo, R. V., Crit. Rev. Biochem. Mol. Biol., 32(2):141-174 (1997). Others studies implicating leucine rich proteins in wound healing and tissue repair are De La Salle, C., et al., Vouv. Rev. Fr. Hematol. (Germany), 37(4):215-222 (1995), reporting mutations in the leucine rich motif in a complex associated with the bleeding disorder Bernard-Soulier syndrome, Chlemetson, K. J., Thromb.

Haemost. (Germany), 74(1):111-116 (July 1995), reporting that platelets have leucine rich repeats and Ruoslahti, E. I., et al., WO9110727-A by La Jolla Cancer Research Foundation reporting that decorin binding to transforming growth factor $\beta$  has involvement in a treatment for cancer, wound healing and scarring. Related by function to this group of proteins is the insulin like growth factor (IGF), in that it is useful in wound-healing and associated therapies concerned with re-growth of tissue, such as connective tissue, skin and bone; in promoting  
 5 body growth in humans and animals; and in stimulating other growth-related processes. The acid labile subunit of IGF (ALS) is also of interest in that it increases the half-life of IGF and is part of the IGF complex in vivo.

Another protein which has been reported to have leucine-rich repeats is the SLIT protein which has been reported to be useful in treating neuro-degenerative diseases such as Alzheimer's disease, nerve damage such as in Parkinson's disease, and for diagnosis of cancer, see, Artavanistsakonas, S. and Rothberg, J. M.,  
 10 WO9210518-A1 by Yale University. Of particular interest is LIG-1, a membrane glycoprotein that is expressed specifically in glial cells in the mouse brain, and has leucine rich repeats and immunoglobulin-like domains. Suzuki, et al., J. Biol. Chem. (U.S.), 271(37):22522 (1996). Other studies reporting on the biological functions of proteins having leucine rich repeats include: Tayar, N., et al., Mol. Cell Endocrinol., (Ireland), 125(1-2):65-70 (Dec. 1996) (gonadotropinreceptor involvement); Miura, Y., et al., Nippon Rinsho (Japan), 54(7):1784-1789  
 15 (July 1996) (apoptosis involvement); Harris, P. C., et al., J. Am. Soc. Nephrol., 6(4):1125-1133 (Oct. 1995) (kidney disease involvement).

We herein describe the identification and characterization of novel polypeptides having homology to LIG, designated herein as PRO1111 polypeptides.

## 20 65. PRO1344

Factor C is a protein that is intimately involved with the coagulation cascade in a variety of organisms. The coagulation cascade has been shown to involve numerous different intermediate proteins, including factor C, all of whose activity is essential to the proper functioning of this cascade. Abnormal coagulation cascade function can result in a variety of serious abnormalities and, as such, the activities of the coagulation cascade  
 25 proteins is of particular interest. As such, efforts are currently being undertaken to identify novel polypeptides having homology to one or more of the coagulation cascade proteins.

We herein describe the identification and characterization of novel polypeptides having homology to factor C protein, designated herein as PRO1344 polypeptides.

## 30 66. PRO1109

Carbohydrate chains on glycoproteins are important not only for protein conformation, transport and stability, but also for cell-cell and cell-matrix interactions.  $\beta$ -1,4-galactosyltransferase is an enzyme that is involved in producing carbohydrate chains on proteins, wherein the  $\beta$ -1,4-galactosyltransferase enzyme acts to transfer galactose to the terminal N-acetylglucosamine of complex-type N-glycans in the Golgi apparatus (Asano  
 35 et al., EMBO J. 16:1850-1857 (1997)). In addition, it has been suggested that  $\beta$ -1,4-galactosyltransferase is involved directly in cell-cell interactions during fertilization and early embryogenesis through a subpopulation of this enzyme distributed on the cell surface. Specifically, Lu et al., Development 124:4121-4131 (1997) and

Larson et al., Biol. Reprod. 57:442-453 (1997) have demonstrated that  $\beta$ -1,4-galactosyltransferase is expressed on the surface of sperm from a variety of mammalian species, thereby suggesting an important role in fertilization. In light of the above, novel polypeptides having sequence identity to  $\beta$ -1,4-galactosyltransferase are of interest.

We herein describe the identification and characterization of novel polypeptides having homology to  $\beta$ -1,4-galactosyltransferase, designated herein as PRO1109 polypeptides.

67. **PRO1383**

The *nmb* gene is a novel gene that encodes a putative transmembrane glycoprotein which is differentially expressed in metastatic human melanoma cell lines and which shows substantial homology to the precursor of pMEL17, a melanocyte-specific protein (Weterman et al., Int. J. Cancer 60:73-81 (1995)). Given the interest in identifying tumor-specific cell-surface polypeptide markers, there is substantial interest in novel polypeptides having homology to *nmb*. We herein describe the identification and characterization of novel polypeptides having homology to the *nmb* protein, designated herein as PRO1383 polypeptides.

15 68. **PRO1003**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1003 polypeptides.

20 69. **PRO1108**

Lysophosphatidic acid acyltransferase (LPAAT) is an enzyme that in lipid metabolism converts lysophosphatidic acid (LPA) into phosphatidic acid (PA). LPA is a phospholipid that acts as an intermediate in membrane phospholipid metabolism. Various LPAAT enzymes have been identified in a variety of species (see, e.g., Aguado et al., J. Biol. Chem. 273:4096-4105 (1998), Stamps et al., Biochem. J. 326:455-461 (1997), Eberhart et al., J. Biol. Chem. 272:20299-20305 (1997) and West et al., DNA Cell Biol. 16:691-701 (1997)). Given the obvious importance of LPAAT in a variety of different applications including cell membrane maintenance, there is substantial interest in identifying and characterizing novel polypeptides having homology to LPAAT. We herein describe the identification and characterization of novel polypeptides having homology to LPAAT protein, designated herein as PRO1108 polypeptides.

30 70. **PRO1137**

A particular class of secreted polypeptides that are of interest in research and industry are ribosyltransferases. Braren et al. described the use of EST databases for the identification and cloning of novel ribosyltransferase gene family members (Adv. Exp. Med. Biol. 419:163-168 (1997)). Ribosyltransferases have been identified playing roles in a variety of metabolic functions including posttranslational modification of proteins (Saxty et al., J. Leukoc. Biol., 63(1):15-21 (1998)), and mediation of the assembly of filamentous actin

and chemotaxis in polymorphonuclear neutrophil leukocytes (Kefalas et al. Adv. Exp. Med. Biol. 419:241-244 (1997)).

Described herein is the identification and characterization of novel polypeptides having homology to ribosyltransferase, designated herein as PRO1137 polypeptides.

5    71.    **PRO1138**

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. Of particular interest is the identification of membrane-bound proteins found in cells of the hematopoietic system, as they often play important roles in fighting infection, repair of  
10    injured tissues, and other activities of cells of the hematopoietic system. For instance, CD84 leukocyte antigen has recently been identified as a new member of the Ig superfamily (de la Fuente *et al.*, Blood, 90(6):2398-2405 (1997)).

Described herein is the identification and characterization of a novel polypeptide having homology to CD84 leukocyte antigen, designated herein as PRO1138 polypeptides.

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72.    **PRO1054**

The proteins of the major urinary protein complex (MUP), proteins which are members of the lipocalin family, function to bind to volatile pheromones and interact with the vomeronasal neuroepithelium of the olfactory system. As such, proteins in the MUP family are intimately involved in the process of attraction  
20    between mammals of different sexes. Many different MUP family members have been identified and characterized and shown to possess varying degrees of amino acid sequence homology (see, e.g., Mucignat et al., Chem. Senses 23:67-70 (1998), Ferrari et al., FEBS Lett. 401:73-77 (1997) and Bishop et al., EMBO J. 1:615-620 (1982)). Given the physiological and biological importance of the MUP family of proteins, there is significant interest in identifying and characterizing novel members of this family. We herein describe the  
25    identification and characterization of novel polypeptides having homology to MUP family of proteins, designated herein as PRO1054 polypeptides.

73.    **PRO994**

The L6 cell surface antigen, which is highly expressed on lung, breast, colon, and ovarian carcinomas,  
30    has attracted attention as a potential therapeutic target for murine monoclonal antibodies and their humanized counterparts (Marken et al., Proc. Natl. Acad. Sci. USA 89:3503-3507 (1992)). The cDNA encoding this tumor-associated cell surface antigen has been expressed in COS cells and shown to encode a 202 amino acid polypeptide having three transmembrane domains. The L6 antigen has been shown to be related to a number of cell surface proteins that have been implicated in the regulation of cell growth, including for example CD63  
35    and CO-029, proteins which are also highly expressed on tumor cells. As such, there is significant interest in identifying novel polypeptides having homology to the L6 tumor cell antigen as potential targets for cancer therapy. We herein describe the identification and characterization of novel polypeptides having homology to



the L6 cell surface tumor cell-associated antigen, designated herein as PRO994 polypeptides.

74. **PRO812**

Steroid binding proteins play important roles in numerous physiological processes associated with steroid function. Specifically, one steroid binding protein-associated polypeptide that has been well characterized is component 1 of the prostatic binding protein. Component 1 of the prostatic binding protein has been shown to be specific for subunit F of the prostatic binding protein, the major secretory glycoprotein of the rat ventral prostate (Peeters et al., Eur. J. Biochem. 123:55-62 (1982) and Liao et al., J. Biol. Chem. 257:122-125 (1982)). The amino acid sequence of component 1 of the prostatic binding protein has been determined, wherein the sequence is highly rich in glutamic acid residues and is overall highly acidic. This protein plays an important role in the response of the prostate gland to steroid hormones. We herein describe the identification and characterization of novel polypeptides having homology to prostatic steroid-binding protein c1, designated herein as PRO812 polypeptides.

75. **PRO1069**

Of particular interest is the identification of new membrane-bound proteins involved in ion conductance such as channel inhibitory factor (CHIF) and MAT-8, which have recently been reported (see Wald et al., Am. J. Physiol. 272(5 pt 2): F617-F623 (1997); Capurro et al., Am. J. Physiol. 271(3 pt 1): C753-C762 (1996); Wald et al., Am. J. Physiol. 271(2 pt 2): F322-F329 (1996); and Morrison et al., J. Biol. Chem. 270(5):2176-2182 (1995)).

Described herein is the identification and characterization of novel polypeptides having homology to CHIF and MAT-8 polypeptides, designated herein as PRO1069 polypeptides.

76. **PRO1129**

Cytochromes P-450 are a superfamily of hemoproteins which represent the main pathway for drug and chemical oxidation (Horsmans, Acta Gastroenterol. Belg. 60:2-10 (1997)). This superfamily is divided into families, subfamilies and/or single enzymes. Recent reports have provided a great deal of information concerning the cytochrome P-450 isozymes and increased awareness of life threatening interactions with such commonly prescribed drugs as cisapride and some antihistamines (Michalets, Pharmacotherapy 18:84-112 (1998) and Singer et al., J. Am. Acad. Dermatol. 37:765-771 (1997)). Given this information, there is significant interest in identifying novel members of the cytochrome P-450 family of proteins. We herein describe the identification and characterization of novel polypeptides having homology to cytochrome P-450 proteins, designated herein as PRO1129 polypeptides.

77. **PRO1068**

Urotensins are neurosecretory proteins that are of interest because of their potential roles in a variety of physiological processes including smooth muscle contraction (Yano et al. Gen. Comp. Endocrinol. 96(3): 412-413 (1994)), regulation of arterial blood pressure and heart rate (Le Mevel et al. Am. J. Physiol. 271(5 Pt 2):

R1335-R1343 (1996)), and corticosteroid secretion (Feuilloley et al. J. Steroid Biochem Mol. Biol. 48(2-3): 287-292 (1994)).

We herein describe the identification and characterization of novel polypeptides having homology to urotensin, designated herein as PRO1068 polypeptides.

5    78.    **PRO1066**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1066 polypeptides.

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79.    **PRO1184**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1184 polypeptides.

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80.    **PRO1360**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1360 polypeptides.

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81.    **PRO1029**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1029 polypeptides.

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82.    **PRO1139**

Obesity is the most common nutritional disorder which, according to recent epidemiologic studies, affects about one third of all Americans 20 years of age or older. Kuczmarski et al., J. Am. Med. Assoc. 272, 205-11 (1994). Obesity is responsible for a variety of serious health problems, including cardiovascular disorders, type II diabetes, insulin-resistance, hypertension, hypertriglyceridemia, dyslipoproteinemia, and some forms of cancer. Pi-Sunyer, F.X., Anns. Int. Med. 119, 655-60 (1993); Colfitz, G.A., Am. J. Clin. Nutr. 55, 503S-507S (1992). A single-gene mutation (the obesity or "ob" mutation) has been shown to result in obesity and type II diabetes in mice. Friedman, Genomics 11, 1054-1062 (1991). Zhang et al., Nature 372, 425-431 (1994) have recently reported the cloning and sequencing of the mouse *ob* gene and its human homologue, and

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suggested that the *ob* gene product may function as part of a signaling pathway from adipose tissue that acts to regulate the size of the body fat depot. Parabiosis experiments performed more than 20 years ago predicted that the genetically obese mouse containing two mutant copies of the *ob* gene (*ob/ob* mouse) does not produce a satiety factor which regulates its food intake, while the diabetic (*db/db*) mouse produces but does not respond to a satiety factor. Coleman and Hummal, Am. J. Physiol. 217, 1298-1304 (1969); Coleman, Diabetol. 9, 294-98 (1973). OB proteins are disclosed, for example, in U.S. patent Nos. 5,532,336; 5,552,522; 5,552,523; 5,552,514; 5,554,727. Recent reports by three independent research teams have demonstrated that daily injections of recombinant OB protein inhibit food intake and reduce body weight and fat in grossly obese *ob/ob* mice but not in *db/db* mice (Pellemounter et al., Science 269, 540-43 [1995]; Halaas et al., Science 269, 543-46 [1995]; Campfield et al., Science 269, 546-49 [1995]), suggesting that the *ob* protein is such a satiety factor as proposed in early cross-circulation studies.

A receptor of the OB protein (OB-R) is disclosed in Tartaglia et al., Cell 83, 1263-71 (1995). The OB-R is a single membrane-spanning receptor homologous to members of the class I cytokine receptor family (Tartaglia et al., *supra*; Bazan, Proc. Natl. Acad. Sci. USA 87, 6934-6938 [1990]). Two 5'-untranslated regions and several 3'-alternative splice variants encoding OB-R with cytoplasmic domains of different lengths have been described in mouse, rat and human (Chen et al., Cell 84, 491-495 [1996]; Chua et al., Science 271, 994-996 [1996]; Tartaglia et al., *supra*; Wang et al., FEBS Lett. 392:87-90 [1996]; Phillips et al., Nature Genet. 13, 18-19 [1996]; Cioffi et al., Nature Med., 2 585-589 [1996]). A human hematopoietin receptor, which might be a receptor of the OB protein, is described in PCT application Publication No. WO 96/08510, published 21 March 1996.

Bailleul et al., Nucl. Acids Res. 25, 2752-2758 (1997) identified a human mRNA splice variant of the OB-R gene that potentially encodes a novel protein, designated as leptin receptor gene-related protein (OB-RGRP). This protein displays no sequence similarity to the leptin receptor itself. The authors found that the OB-RGRP gene shares its promoter and two exons with the OB-R gene, and suggested that there is a requirement for a coordinate expression of OB-R and OB-RGRP to elicit the full physiological response to leptin *in vivo*.

### 83. PRO1309

Protein-protein interactions include receptor and antigen complexes and signaling mechanisms. As more is known about the structural and functional mechanisms underlying protein-protein interactions, protein-protein interactions can be more easily manipulated to regulate the particular result of the protein-protein interaction. Thus, the underlying mechanisms of protein-protein interactions are of interest to the scientific and medical community.

All proteins containing leucine-rich repeats are thought to be involved in protein-protein interactions. Leucine-rich repeats are short sequence motifs present in a number of proteins with diverse functions and cellular locations. The crystal structure of ribonuclease inhibitor protein has revealed that leucine-rich repeats correspond to beta-alpha structural units. These units are arranged so that they form a parallel beta-sheet with one surface exposed to solvent, so that the protein acquires an unusual, nonglobular shape. These two features have been indicated as responsible for the protein-binding functions of proteins containing leucine-rich repeats.

See, Kobe and Deisenhofer, Trends Biochem. Sci., 19(10):415-421 (Oct. 1994); Kobe and Deisenhofer, Curr. Opin. Struct. Biol., 5(3):409-416 (1995).

A study has been reported on leucine-rich proteoglycans which serve as tissue organizers, orienting and ordering collagen fibrils during ontogeny and are involved in pathological processes such as wound healing, tissue repair, and tumor stroma formation. Iozzo, R. V., Crit. Rev. Biochem. Mol. Biol., 32(2):141-174 (1997). Others studies implicating leucine rich proteins in wound healing and tissue repair are De La Salle, C., et al., Vouv. Rev. Fr. Hematol. (Germany), 37(4):215-222 (1995), reporting mutations in the leucine rich motif in a complex associated with the bleeding disorder Bernard-Soulier syndrome, Chlemetson, K. J., Thromb. Haemost. (Germany), 74(1):111-116 (July 1995), reporting that platelets have leucine rich repeats and Ruoslahti, E. I., et al., WO9110727-A by La Jolla Cancer Research Foundation reporting that decorin binding to transforming growth factor $\beta$  has involvement in a treatment for cancer, wound healing and scarring. Related by function to this group of proteins is the insulin like growth factor (IGF), in that it is useful in wound-healing and associated therapies concerned with re-growth of tissue, such as connective tissue, skin and bone; in promoting body growth in humans and animals; and in stimulating other growth-related processes. The acid labile subunit of IGF (ALS) is also of interest in that it increases the half-life of IGF and is part of the IGF complex in vivo.

Another protein which has been reported to have leucine-rich repeats is the SLIT protein which has been reported to be useful in treating neuro-degenerative diseases such as Alzheimer's disease, nerve damage such as in Parkinson's disease, and for diagnosis of cancer, see, Artavanistsakonas, S. and Rothberg, J. M., WO9210518-A1 by Yale University. Of particular interest is LIG-1, a membrane glycoprotein that is expressed specifically in glial cells in the mouse brain, and has leucine rich repeats and immunoglobulin-like domains. Suzuki, et al., J. Biol. Chem. (U.S.), 271(37):22522 (1996). Other studies reporting on the biological functions of proteins having leucine rich repeats include: Tayar, N., et al., Mol. Cell Endocrinol., (Ireland), 125(1-2):65-70 (Dec. 1996) (gonadotropin receptor involvement); Miura, Y., et al., Nippon Rinsho (Japan), 54(7):1784-1789 (July 1996) (apoptosis involvement); Harris, P. C., et al., J. Am. Soc. Nephrol., 6(4):1125-1133 (Oct. 1995) (kidney disease involvement).

Efforts are therefore being undertaken by both industry and academia to identify new proteins having leucine rich repeats to better understand protein-protein interactions. Of particular interest are those proteins having leucine rich repeats and homology to known proteins having leucine rich repeats such as platelet glycoprotein V, SLIT and ALS. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins having leucine rich repeats.

#### 84. PRO1028

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1028 polypeptides.

**85. PRO1027**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1027 polypeptides.

**86. PRO1107**

Of particular interest are novel proteins having some sequence identity to known proteins. Known proteins include PC-1, an ecto-enzyme possessing alkaline phosphodiesterase I and nucleotide pyrophosphatase activities, further described in Belli et al., Eur. J. Biochem., 228(3):669-676 (1995). Phosphodiesterases are also described in Fuss et al., J. Neurosci., 17(23):9095-9103 (1997) and Scott et al., Hepatology, 25(4):995-1002 (1997). Phosphodiesterase I, is described as a novel adhesin molecule and/or cytokine (related to autotaxin) involved in oligodendrocyte function. Fuss, supra.

We herein describe the identification and characterization of novel polypeptides having homology to PC-1, designated herein as PRO1107 polypeptides.

**87. PRO1140**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1140 polypeptides.

**88. PRO1106**

As the mitochondria is primarily responsible for generating energy, proteins associated with the mitochondria are of interest. Recently, a cDNA from a novel  $\text{Ca}^{++}$ -dependent member of the mitochondrial solute carrier superfamily was isolated from a rabbit small intestinal cDNA library as described in Weber, et al., PNAS USA, 94(16):8509-8514 (1997). It was reported that this transporter has four elongation factor-hand motifs in the N-terminal and is localized in the peroxisome, although a fraction can be found in the mitochondria. Thus, this transporter, and proteins which have sequence identity to this and other members of the mitochondrial solute carrier superfamily are of particular interest.

We herein describe the identification and characterization of novel polypeptides having homology to a peroxisomal calcium dependent solute carrier protein, designated herein as PRO1106 polypeptides.

**89. PRO1291**

Butyrophilin is a milk glycoprotein that constitutes more than 40% of the total protein associated with the fat globule membrane in mammalian milk. Expression of butyrophilin mRNA has been shown to correlate with the onset of milk fat production toward the end pregnancy and is maintained throughout lactation. Butyrophilin has been identified in bovine, murine and human (see Taylor et al., Biochim. Biophys. Acta

1306:1-4 (1996), Ishii et al., Biochim. Biophys. Acta 1245:285-292 (1995), Mather et al., J. Dairy Sci. 76:3832-3850 (1993) and Banghart et al., J. Biol. Chem. 273:4171-4179 (1998)) and is a type I transmembrane protein that is incorporated into the fat globulin membrane. It has been suggested that butyrophilin may play a role as the principle scaffold for the assembly of a complex with xanthine dehydrogenase/oxidase and other proteins that function in the budding and release of milk-fat globules from the apical surface during lactation (Banghart et al., supra).

Given that butyrophilin plays an obviously important role in mammalian milk production, there is substantial interest in identifying novel butyrophilin homologs. We herein describe the identification and characterization of novel polypeptides having homology to butyrophilin, designated herein as PRO1291 polypeptides.

#### 90. PRO1105

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1105 polypeptides.

#### 91. PRO511

Proteins of interest include those having sequence identity with RoBo-1, a novel member of the urokinase plasminogen activator receptor/CD59/Ly-6/snake toxin family selectively expressed in bone and growth plate cartilage as described in Noel et al., J. Biol. Chem. 273(7):3878-3883 (1998). RoBo-1 is believed to play a novel role in the growth or remodeling of bone. Proteins also of interest include those having sequence identity with phospholipase inhibitors.

We herein describe the identification and characterization of novel polypeptides having homology to urokinase plasminogen activator receptors and phospholipase inhibitors, designated herein as PRO511 polypeptides.

#### 92. PRO1104

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1104 polypeptides.

#### 93. PRO1100

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1100 polypeptides.



**94.     PRO836**

Of interest are luminal proteins, or proteins specific to the endoplasmic reticulum (ER). Of particular interest are proteins having sequence identity with known proteins. Known proteins include proteins such as SLS1. In *Saccharomyces cerevisiae*, SLS1 has been reported to be a mitochondrial integral membrane protein involved in mitochondrial metabolism. Rouillard, et al., Mol. Gen. Genet., 252(6):700-708 (1996). In yeast  
5 *Yarrowia lipolytica*, it has been reported that the SLS1 gene product (SLS1p) behaves as a luminal protein of the ER. It is believed that SPS1p acts in the preprotein translocation process, interacting directly with translocating polypeptides to facilitate their transfer and/or help their folding in the ER. Bosirame, et al., J. Biol. Chem., 271(20):11668-11675 (1996).

We herein describe the identification and characterization of novel polypeptides having homology to  
10 SLS1, designated herein as PRO836 polypeptides.

**95.     PRO1141**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to  
15 identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1141 polypeptides.

**96.     PRO1132**

Proteases are enzymatic proteins which are involved in a large number of very important biological  
20 processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized, including the serine proteases which exhibit specific activity toward various serine-containing proteins. The mammalian protease enzymes play important roles in biological processes such as, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and  
25 enzymes.

Neuropsin is a novel serine protease whose mRNA is expressed in the central nervous system. Mouse neuropsin has been cloned, and studies have shown that it is involved in the hippocampal plasticity. Neuropsin has also been indicated as associated with extracellular matrix modifications and cell migrations. See, generally, Chen, et al., Neurosci., 7(2):5088-5097 (1995) and Chen, et al., J. Histochem. Cytochem., 46:313-320 (1998).

Another serine protease of interest is the enamel matrix serine proteinase. The maturation of dental enamel succeeds the degradation of organic matrix. Inhibition studies have shown that this degradation is accomplished by a serine-type proteinase. Proteases associated with enamel maturation are described in, i.e., Simmer, et al., J. Dent. Res., 77(2):377-386 (1998), Overall and Limeback, Biochem J., 256(3):965-972 (1988), and Moradian-Oldak, Connect. Tissue Res., 35(1-4):231-238 (1996).  
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We herein describe the identification and characterization of novel polypeptides having homology to serine proteases, designated herein as PRO1132 polypeptides.  
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97. PRO1346

The abbreviations "TIE" or "tie" are acronyms, which stand for "tyrosine kinase containing Ig and EGF homology domains" and were coined to designate a new family of receptor tyrosine kinases which are almost exclusively expressed in vascular endothelial cells and early hemopoietic cells, and are characterized by the presence of an EGF-like domain, and extracellular folding units stabilized by intra-chain disulfide bonds, generally referred to as "immunoglobulin (IG)-like" folds. A tyrosine kinase homologous cDNA fragment from human leukemia cells (tie) was described by Partanen et al., Proc. Natl. Acad. Sci. USA **87**, 8913-8917 (1990). The mRNA of this human "TIE" receptor has been detected in all human fetal and mouse embryonic tissues, and has been reported to be localized in the cardiac and vascular endothelial cells. Korhonen et al., Blood **80**, 2548-2555 (1992); PCT Application Publication No. WO 93/14124 (published 22 July 1993). The rat homolog of human TIE, referred to as "TIE-1", was identified by Maisonpierre et al., Oncogene **8**, 1631-1637 (1993)). Another TIE receptor, designated "TIE-2" was originally identified in rats (Dumont et al., Oncogene **8**, 1293-1301 (1993)), while the human homolog of TIE-2, referred to as "ork" was described in U.S. Patent No. 5,447,860 (Ziegler). The murine homolog of TIE-2 was originally termed "tek." The cloning of a mouse TIE-2 receptor from a brain capillary cDNA library is disclosed in PCT Application Publication No. WO 95/13387 (published 18 May 1995). TIE-2 is a receptor tyrosine kinase that is expressed almost exclusively by vascular endothelium. Tie-2 knockout mice die by defects in the formation of microvassels. Accordingly, the TIE receptors are believed to be actively involved in angiogenesis, and may play a role in hemopoiesis as well. Indeed, recent results (Lin *et al.*, J. Clin. Invest. **100**(8), 2072-2078 [1997]) demonstrating the ability of a soluble TIE-2 receptor to inhibit tumor angiogenesis have been interpreted to indicate that TIE-2 plays a role in pathologic vascular growth. In another study, TIE-2 expression was examined in adult tissues undergoing angiogenesis and in quiescent tissues. TIE2 expression was localized by immunohistochemistry to the endothelium of neovessels in rat tissues undergoing angiogenesis during hormonally stimulated follicular maturation and uterine development and in healing wounds. TIE-2 was also reported to be expressed in the entire spectrum of the quiescent vasculature (arteries, veins, and capillaries) in a wide range of adult tissues. Wong *et al.*, Circ. Res. **81**(4), 567-574 (1997). It has been suggested that TIE-2 has a dual function in adult angiogenesis and vascular maintenance.

The expression cloning of human TIE-2 ligands has been described in PCT Application Publication No. WO 96/11269 (published 18 April 1996) and in U.S. Patent No. 5,521,073 (published 28 May 1996). A vector designated as  $\lambda$ gt10 encoding a TIE-2 ligand NL7d "htie-2 ligand 1" or "hTL1" has been deposited under ATCC Accession No. 75928. A plasmid encoding another TIE-2 ligand designated "htie-2 2" or "hTL2" is available under ATCC Accession No. 75928. This second ligand has been described as an antagonist of the TAI-2 receptor. The identification of secreted human and mouse ligands for the TIE-2 receptor has been reported by Davis et al., Cell **87**, 1161-1169 (1996). The human ligand designated "Angiopoietin-1", to reflect its role in angiogenesis and potential action during hemopoiesis, is the same ligand as the ligand variously designated as "htie-2 1" or "hTL-1" in WO 96/11269. Angiopoietin-1 has been described to play an angiogenic role later and distinct from that of VEGF (Suri et al., Cell **87**, 1171-1180 (1996)). Since TIE-2 is apparently upregulated during the pathologic angiogenesis requisite for tumor growth (Kaipainen et al., Cancer Res. **54**, 6571-6577

(1994)) angiopoietin-1 has been suggested to be additionally useful for specifically targeting tumor vasculature (Davis et al., supra).

We herein describe the identification and characterization of novel TIE ligand polypeptides, designated herein as PRO1346 polypeptides.

5 98. PRO1131

The low density lipoprotein (LDL) receptor is a membrane-bound protein that plays a key role in cholesterol homeostasis, mediating cellular uptake of lipoprotein particles by high affinity binding to its ligands, apolipoprotein (apo) B-100 and apoE. The ligand-binding domain of the LDL receptor contains 7 cysteine-rich repeats of approximately 40 amino acids, wherein each repeat contains 6 cysteines, which form 3 intra-repeat  
10 disulfide bonds. These unique structural features provide the LDL receptor with its ability to specifically interact with apo B-100 and apoE, thereby allowing for transport of these lipoprotein particles across cellular membranes and metabolism of their components. Soluble fragments containing the extracellular domain of the LDL receptor have been shown to retain the ability to interact with its specific lipoprotein ligands (Simmons et al., J. Biol. Chem. 272:25531-25536 (1997)). LDL receptors are further described in Javitt, FASEB J., 9(13):1378-1381  
15 (1995), van Berkel, et al., Atherosclerosis, 118 Suppl:S43-S50 (1995) and Herz and Willnow, Ann. NY Acad. Sci., 737:14-19 (1994). Thus, proteins having sequence identity with LDL receptors are of interest.

We herein describe the identification and characterization of novel polypeptides having homology to LDL receptors, designated herein as PRO1131 polypeptides.

20 99. PRO1281

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel  
25 secreted polypeptides, designated herein as PRO1281 polypeptides.

100. PRO1064

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel membrane-bound proteins. We herein describe the identification and  
30 characterization of novel transmembrane polypeptides, designated herein as PRO1064 polypeptides.

101. PRO1379

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the  
35 coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1379 polypeptides.

**102. PRO844**

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized. The mammalian protease enzymes play important roles in many different biological processes including, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes. Thus, proteases are of interest. Also of interest are protease inhibitors.

Of particular interest are serine proteases. In one study it was reported that when the serine protease inhibitor antileukoproteinase (aLP) is injected, it accumulates in articular and extraarticular cartilage of normal rats. This physiological pathway of cartilage accumulation, lost in proteoglycan depleted arthritic cartilage is believed to serve to maintain the local balance between proteinase function and inhibition. Burkhardt, et al., J. Rheumatol., 24(6):1145-1154 (1997). Moreover, aLP and other protease inhibitors have been reported to play a role in the in vitro growth of hematopoietic cells by the neutralization of proteinases produced by bone marrow accessory cells. Gosklink, et al., J. Exp. Med., 184(4):1305-1312 (1996). Also of interest are mutants of aLP. Oxidation resistant mutants of aLP have been reported to have significant therapeutic effects on animal models having emphysema. Steffens, et al., Agents Actions Suppl., 42:111-121 (1993). Thus, serine protease inhibitors are of interest.

We herein describe the identification and characterization of novel polypeptides having homology to serine protease inhibitors, designated herein as PRO844 polypeptides.

**103. PRO848**

Membrane-bound proteins of interest include channels such as ion channels. Furthermore, membrane-bound proteins of interest include enzymes bound to intracellular vacuoles or organelles, such as transferases. For example, a peptide of interest is the GalNAc alpha 2, 6-sialyltransferase as described in Kurosawa, et al., J. Biol. Chem., 269(2):1402-1409 (1994). This peptide was constructed to be secreted, and retained its catalytic activity. The expressed enzyme exhibited activity toward asialomucin and asialofetuin, but not other glycoproteins tested. As sialylation is an important function, sialyltransferases such as this one, and peptides related by sequence identity, are of interest.

We herein describe the identification and characterization of novel polypeptides having homology to sialyltransferases, designated herein as PRO848 polypeptides.

**104. PRO1097**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1097 polypeptides.



**105. PRO1153**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel transmembrane proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1153 polypeptides.

**106. PRO1154**

Aminopeptidase N causes enzymatic degradation of perorally administered peptide drugs. Thus, aminopeptidase N has been used in studies to develop and identify inhibitors so as to increase the efficacy of peptide drugs by inhibiting their degradation. Aminopeptidases are also generally of interest to use to degrade peptides. Aminopeptidases, particularly novel aminopeptidases are therefore of interest. Aminopeptidase N and inhibitors thereof are further described in Bernkop-Schnurch and Marschutz, Pharm. Res., 14(2):181-185 ((1997); Lerche, et al., Mamm. Genome, 7(9):712-713 (1996); Papapetropoulos, et al., Immunopharmacology, 32(1-3):153-156 (1996); Miyachi, et al., J. Med. Chem., 41(3):263-265 (1998); and Olsen, et al., Adv. Exp. Med. Biol., 421:47-57 (1997).

We herein describe the identification and characterization of novel polypeptides having homology to aminopeptidase N, designated herein as PRO1154 polypeptides.

**107. PRO1181**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1181 polypeptides.

**108. PRO1182**

Conglutinin is a bovine serum protein that was originally described as a vertebrate lectin protein and which belongs to the family of C-type lectins that have four characteristic domains, (1) an N-terminal cysteine-rich domain, (2) a collagen-like domain, (3) a neck domain and (4) a carbohydrate recognition domain (CRD). Recent reports have demonstrated that bovine conglutinin can inhibit hemagglutination by influenza A viruses as a result of their lectin properties (Eda et al., Biochem. J. 316:43-48 (1996)). It has also been suggested that lectins such as conglutinin can function as immunoglobulin-independent defense molecules due to complement-mediated mechanisms. Thus, conglutinin has been shown to be useful for purifying immune complexes *in vitro* and for removing circulating immune complexes from patients plasma *in vivo* (Lim et al., Biochem. Biophys. Res. Commun. 218:260-266 (1996)). We herein describe the identification and characterization of novel polypeptides having homology to conglutinin protein, designated herein as PRO1182 polypeptides.

**109. PRO1155**

Substance P and the related proteins, neurokinin A and neurokinin B have been reported as compounds which elicit contraction of the ileum both directly through action on a muscle cell receptor and indirectly through stimulation of a neuronal receptor. This action leads to the release of acetylcholine which causes muscle contraction via muscarinic receptors. It has also been reported that neurokinin B was found to be the most potent agonist for the neuronal Substance P receptor and that neurokinin B can be inhibited by enkephalinamide. Laufer, et al., PNAS USA, 82(21):74444-7448 (1985). Moreover, neurokinin B has been reported to provide neuroprotection and cognitive enhancement, and therefore believed to be useful for the treatment of neurodegenerative disorders, including alzheimers disease. Wenk, et al., Behav. Brain Res., 83(1-2):129-133 (1997). Tachykinins are also described in Chawla, et al., J. Comp. Neurol., 384(3):429-442 (1997). Thus, tachykinins, particularly those related to neurokinin B are of interest.

We herein describe the identification and characterization of novel polypeptides having homology to neurokinin B protein, designated herein as PRO1155 polypeptides.

**110. PRO1156**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1181 polypeptides.

**111. PRO1098**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1098 polypeptides.

**112. PRO1127**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1127 polypeptides.

**113. PRO1126**

The extracellular mucous matrix of olfactory neuroepithelium is a highly organized structure in intimate contact with chemosensory cilia that house the olfactory transduction machinery. The major protein component of this extracellular matrix is olfactomedin, a glycoprotein that is expressed in olfactory neuroepithelium and which form intermolecular disulfide bonds so as to produce a polymer (Yokoe et al., Proc. Natl. Acad. Sci. USA 90:4655-4659 (1993), Bal et al., Biochemistry 32:1047-1053 (1993) and Snyder et al., Biochemistry 30:9143-

9153 (1991)). It has been suggested that olfactomedin may influence the maintenance, growth or differentiation of chemosensory cilia on the apical dendrites of olfactory neurons. Given this important role, there is significant interest in identifying and characterizing novel polypeptides having homology to olfactomedin. We herein describe the identification and characterization of novel polypeptides having homology to olfactomedin protein, designated herein as PRO1126 polypeptides.

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**114. PRO1125**

Of particular interest are proteins which have multiple Trp-Asp (WD) repeats. WD proteins are made up of highly conserved repeating units usually ending with WD. They are found in eukaryotes but not in prokaryotes. They regulate cellular functions, such as cell division, cell-fate determination, gene transcription, gene transcription, transmembrane signaling, mRNA modification and vesicle fusion. WD are further described in Neer, et al., Nature, 371(6495):297-300 (1994); Jiang and Struhl, Nature, 391(6666):493-496(1998); and DeSilva, et al., Genetics, 148(2):657-667 (1998). Thus, new members of this superfamily are all of interest.

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**115. PRO1186**

Protein A from *Dendroaspis polylepis polylepis* (black mamba) venom comprises 81 amino acids, including ten half-cystine residues. Venoms are of interest on the one hand as weapons in war, and on the other hand, to use in assays to determine agents which reverse or inhibit the effects of the venom or a similar poison. Black mamba venom is further described in Int. J. Biochem., 17(6):695-699 (1985) and Joubert and Strydom, Hoppe Seylers Z Physiol. Chem., 361(12):1787-1794 (1980).

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We herein describe the identification and characterization of novel polypeptides having homology to snake venom protein A, designated herein as PRO1186 polypeptides.

**116. PRO1198**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1198 polypeptides.

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**117. PRO1158**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel transmembrane proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1158 polypeptides.

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**118. PRO1159**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the

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coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1159 polypeptides.

#### 119. PRO1124

Ion channels are considered to be the gateway to the final frontier, the brain. Ion channels and the receptors which control these channels are responsible for the passage of ions, or nerve impulses to be communicated from cell to cell, thus, ion channels are responsible for communication. In addition to their critical role in the brain, ion channels play a critical role in the heart as well as blood pressure. Ion channels have also been linked to other important bodily functions and conditions, as well as disorders, such as cystic fibrosis. For all of these reasons, ion channels, such as sodium, potassium and chloride channels, as well as all of their related proteins and receptors are of interest. For example, it has been reported that cystic fibrosis results from a defect in the chloride channel protein, cystic fibrosis transmembrane conductance regulator. McGill, et al., Dig. Dis. Sci., 41(3):540-542 (1996). Chloride channels are further described in at least Finn, et al., PNAS USA, 90(12):5691-569 (1993) and Finn, et al., Mol. Cell Biochem., 114(1-2):21-26 (1992).

Also of interest are molecules related to adhesion molecules, as adhesion molecules are known to be involved in cell-cell signaling and interactions. More generally, all novel membrane bound-proteins are of interest. Membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, channels, transporters, and cellular adhesion molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins include those which are bound to the outer membrane and intracellular membranes and organelles. Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor proteins. Herein is presented a polypeptide and nucleic acid encoding therefor which has sequence identity with a chloride channel protein chloride channel protein and lung-endothelial cell



adhesion molecule-1 (ECAM-1).

**120. PRO1287**

Fringe is a protein which specifically blocks serrate-mediated activation of notch in the dorsal compartment of the *Drosophila* wing imaginal disc. Fleming et al., Development, 124(15):2973-81 (1997).

5 Therefore, fringe protein is of interest for both its role in development as well as its ability to regulate serrate, particularly serrate's signaling abilities. Also of interest are novel polypeptides which may have a role in development and/or the regulation of serrate-like molecules. Of particular interest are novel polypeptides having homology to fringe.

10 We herein describe the identification and characterization of novel polypeptides having homology to fringe protein, designated herein as PRO1287 polypeptides.

**121. PRO1312**

Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to  
15 identify the coding sequences for novel transmembrane proteins. We herein describe the identification and characterization of novel transmembrane polypeptides, designated herein as PRO1312 polypeptides.

**122. PRO1192**

Membrane-bound proteins of myelin are of interest because of their possible implications in various  
20 nervous system disorders associated with improper myelination. Myelin is a cellular sheath, formed by glial cells, that surrounds axons and axonal processes that enhances various electrochemical properties and provides trophic support to the neuron. Myelin is formed by Schwann cells in the peripheral nervous system (PNS) and by oligodendrocytes in the central nervous system (CNS). Improper myelination of central and peripheral neurons occurs in a number of pathologies and leads to improper signal conduction within the nervous systems.  
25 Among the various demyelinating diseases Multiple Sclerosis is the most notable.

The predominant integral membrane protein of the CNS myelin of amphibians, reptiles, birds and mammals are proteolipid protein (PLP) and P0, the main glycoprotein in PNS myelin. (Schlieess and Stoffel, Biol. Chem. Hoppe Seyler (1991) 372(9):865-874). In view of the importance of membrane-bound proteins of the myelin, efforts are being undertaken by both industry and academia to identify and characterize various  
30 myelin proteins (see Stratmann and Jeserich, J. Neurochem (1995) 64(6):2427-2436).

**123. PRO1160**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the  
35 coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1160 polypeptides.

**124. PRO1187**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1187 polypeptides.

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**125. PRO1185**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1185 polypeptides.

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**126. PRO345**

Human tetranectin is a 202 amino acid protein encoded by a gene spanning approximately 12 kbp of DNA (Berglund et al., FEBS Lett. 309:15-19 (1992)). Tetranectin has been shown to be expressed in a variety of tissues and functions primarily as a plasminogen binding protein. Tetranectin has been classified in a distinct group of the C-type lectin superfamily but has structural and possibly functional similarity to the collectin proteins (Nielsen et al., FEBS Lett. 412(2):388-396 (1997)). Recent studies have reported that variability in serum tetranectin levels may be predictive of the presence of various types of cancers including, for example, ovarian and colorectal cancers (Hogdall et al., Acta Oncol. 35:63-69 (1996), Hogdall et al., Eur. J. Cancer 31A(6):888-894 (1995) and Tuxen et al., Cancer Treat. Rev. 21(3):215-245 (1995)). As such, there is significant interest in identifying and characterizing novel polypeptides having structural and functional similarity to the tetranectin protein.

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We herein describe the identification and characterization of novel polypeptides having homology to tetranectin protein, designated herein as PRO1345 polypeptides.

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**127. PRO1245**

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1245 polypeptides.

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**128. PRO358**

Serine protease inhibitors are of interest because they inhibit catabolism and are sometimes associated with regeneration of tissue. For example, a gene encoding a plasma protein associated with liver regeneration has been cloned and termed regeneration-associated serpin-1 (RASP-1). New, et al., Biochem. Biophys. Res. Commun., 223(2):404-412 (1996). While serine protease inhibitors are of interest, particularly of interest are those which have sequence identity with known serine protease inhibitors such as RASP-1.

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We herein describe the identification and characterization of novel polypeptides having homology to RASP-1, designated herein as PRO1245 polypeptides.

#### 129. PRO1195

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins.

- 5 Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1195 polypeptides.

#### 130. PRO1270

- 10 The recognition of carbohydrates by lectins has been found to play an important role in various aspects of eukaryotic physiology. A number of different animal and plant lectin families exist, but it is the calcium dependent, or type C, lectins that have recently garnered the most attention. For example, the recognition of carbohydrate residues on either endothelial cells or leukocytes by the selectin family of calcium dependent lectins has been found to be of profound importance to the trafficking of leukocytes to inflammatory sites. Lasky, L.,  
 15 Ann. Rev. Biochem., 64 113-139 (1995). The biophysical analysis of these adhesive interactions has suggested that lectin-carbohydrate binding evolved in this case to allow for the adhesion between leukocytes and the endothelium under the high shear conditions of the vasculature. Thus, the rapid on rates of carbohydrate recognition by such lectins allows for a hasty acquisition of ligand, a necessity under the high shear of the vascular flow. The physiological use of type C lectins in this case is also supported by the relatively low affinities  
 20 of these interactions, a requirement for the leukocyte rolling phenomenon that has been observed to occur at sites of acute inflammation. The crystal structures of the mannose binding protein (Weis *et al.*, Science 254, 1608-1615 [1991]; Weis *et al.*, Nature 360 127-134 [1992]) and E-selectin (Graves *et al.*, Nature 367(6463), 532-538 [1994]), together with various mutagenesis analyses (Erbe *et al.*, J. Cell. Biol. 119(1), 215-227 [1992]; Drickamer, Nature 360, 183-186 [1992]; Iobst *et al.*, J. Biol. Chem. 169(22), 15505-15511 [1994]; Kogan *et al.*, J. Biol. Chem. 270(23), 14047-14055 [1995]), is consistent with the supposition that the type C lectins are,  
 25 in general, involved with the rapid recognition of clustered carbohydrates. Together, these data suggest that type C lectins perform a number of critical physiological phenomena through the rapid, relatively low affinity recognition of carbohydrates.

- 30 Given the obvious importance of the lectin proteins in numerous biological processes, efforts are currently being made to identify novel lectin proteins or proteins having sequence homology to lectin proteins. We herein describe the identification and characterization of novel polypeptides having homology to a lectin protein, designated herein as PRO1270 polypeptides.

#### 131. PRO1271

- 35 Efforts are being undertaken by both industry and academia to identify new, native membrane-bound proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel transmembrane proteins. We herein describe the identification and

characterization of novel transmembrane polypeptides, designated herein as PRO1271 polypeptides.

**132. PRO1375**

The proteins L1CAM, G6PD and P55 are each associated with various known disease states. Thus, the genomic loci of *Fugu rubripes* homologs of the human disease genes L1CAM, G6PD and P55 were analyzed.

5 This analysis led to the the identification of putative protein 2 (PUT2), GENBANK locus AF026198, accession AF026198. (See GENBANK submission data). Thus, PUT2 and proteins which have sequence identity with PUT2, are of interest.

**133. PRO1385**

10 Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. We herein describe the identification and characterization of novel secreted polypeptides, designated herein as PRO1385 polypeptides.

**15 134. PRO1387**

Membrane-bound proteins of myelin are of interest because of their possible implications in various nervous system disorders associated with improper myelination. Myelin is a cellular sheath, formed by glial cells, that surrounds axons and axonal processes that enhances various electrochemical properties and provides trophic support to the neuron. Myelin is formed by Schwann cells in the peripheral nervous system (PNS) and  
20 by oligodendrocytes in the central nervous system (CNS). Improper myelination of central and peripheral neurons occurs in a number of pathologies and leads to improper signal conduction within the nervous systems. Among the various demyelinating diseases Multiple Sclerosis is the most notable.

The predominant integral membrane protein of the CNS myelin of amphibians, reptiles, birds and mammals are proteolipid protein (PLP) and P0, the main glycoprotein in PNS myelin. (Schlieess and Stoffel,  
25 Biol. Chem. Hoppe Seyler (1991) 372(9):865-874). In view of the importance of membrane-bound proteins of the myelin, efforts are being undertaken by both industry and academia to identify and characterize various myelin proteins (see Stratmann and Jeserich, J. Neurochem (1995) 64(6):2427-2436).

We herein describe the identification and characterization of novel polypeptides having homology to myelin protein, designated herein as PRO1387 polypeptides.

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**135. PRO1384**

One class of receptor proteins that has been of interest is the NKG2 family of type II transmembrane molecules that are expressed in natural killer cells. These proteins, which have been shown to be covalently associated with CD94, are involved in natural killer cell-mediated recognition of different HLA-allotypes  
35 (Plougastel, B. *et al.*, Eur. J. Immunol. (1997) 27(11):2835-2839), and interact with major histocompatibility complex (MHC) class I to either inhibit or activate functional activity (Ho, EL. *et al.*, Proc. Natl. Acad. Sci. (1998) 95(11):6320-6325). Accordingly, the identification and characterization of new members of this family



of receptor proteins is of interest (see Houchins JP, *et al. J. Exp. Med.* (1991) 173(4):1017-1020).

### SUMMARY OF THE INVENTION

#### 1. PRO281

5 A cDNA clone (DNA16422-1209) has been identified, having homology to nucleic acid encoding testis enhanced gene transcript (TEGT) protein that encodes a novel polypeptide, designated in the present application as "PRO281".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO281 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO281 polypeptide having the sequence of amino acid residues from about 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO281 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 80 or about 122 and about 1114, inclusive, of Figure 1 (SEQ ID NO:1). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209929 (DNA16422-1209) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209929 (DNA16422-1209).

25 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2), or (b) the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO281 polypeptide having the sequence of amino acid residues from 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO281 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 14 in the sequence of Figure 2 (SEQ ID NO:2). The multiple  
5 transmembrane domains have been tentatively identified as extending from about amino acid position 83 to about amino acid position 105, from about amino acid position 126 to about amino acid position 146, from about amino acid position 158 to about amino acid position 177, from about amino acid position 197 to about amino acid position 216, from about amino acid position 218 to about amino acid position 238, from about amino acid position 245 to about amino acid position 265, and from about amino acid position 271 to about amino acid  
10 position 290 in the PRO281 amino acid sequence (Figure 2, SEQ ID NO:2).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2), or (b) the  
15 complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO281 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived  
20 from the nucleotide sequence shown in Figure 1 (SEQ ID NO:1).

In another embodiment, the invention provides isolated PRO281 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO281 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 15 to about 345 of Figure  
25 2 (SEQ ID NO:2).

In another aspect, the invention concerns an isolated PRO281 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2).

30 In a further aspect, the invention concerns an isolated PRO281 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2).

In yet another aspect, the invention concerns an isolated PRO281 polypeptide, comprising the sequence  
35 of amino acid residues 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2), or a fragment thereof sufficient to provide a binding site for an anti-PRO281 antibody. Preferably, the PRO281 fragment retains a qualitative biological activity of a native PRO281 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO281 polypeptide having the sequence of amino acid residues from about 1 or about 15 to about 345, inclusive of Figure 2 (SEQ ID NO:2), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO281 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO281 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO281 polypeptide by contacting the native PRO281 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO281 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

## 2. PRO276

A cDNA clone (DNA16435-1208) has been identified that encodes a novel polypeptide having two transmembrane domains and designated in the present application as "PRO276."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO276 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO276 polypeptide having the sequence of amino acid residues from about 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO276 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 180 and about 932, inclusive, of Figure 3 (SEQ ID NO:5). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209930 (DNA16435-1208), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209930 (DNA16435-1208).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6), or the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO276 polypeptide having the sequence of amino acid residues from about 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably  
10 at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO276 polypeptide in its soluble, i.e. transmembrane domains deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domains are at about amino acids  
15 98-116 and 152-172.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6), or (b) the complement  
20 of the DNA of (a).

Another embodiment is directed to fragments of a PRO276 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

25 In another embodiment, the invention provides isolated PRO276 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO276 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 251 of Figure 4 (SEQ ID NO:6).

In another aspect, the invention concerns an isolated PRO276 polypeptide, comprising an amino acid  
30 sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6).

In a further aspect, the invention concerns an isolated PRO276 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least  
35 about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 251 of Figure 4 (SEQ ID NO:6).



In yet another aspect, the invention concerns an isolated PRO276 polypeptide, comprising the sequence of amino acid residues 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6), or a fragment thereof sufficient to provide a binding site for an anti-PRO276 antibody. Preferably, the PRO276 fragment retains a qualitative biological activity of a native PRO276 polypeptide.

5 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO276 polypeptide having the sequence of amino acid residues from about 1 to about 251, inclusive of Figure 4 (SEQ ID NO:6), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising  
10 the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO276 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO276 antibody.

15 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO276 polypeptide, by contacting the native PRO276 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO276 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 20 3. PRO189

A cDNA clone (DNA21624-1391) has been identified that encodes a novel polypeptide, designated in the present application as "PRO189". PRO189 polypeptides have a cytosolic fatty-acid binding domain.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO189 polypeptide.

25 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO189 polypeptide having the sequence of amino acid residues from about 1 to about 367, inclusive of Figure 6 (SEQ ID NO:8), or (b) the complement of the DNA molecule of (a).

30 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO189 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 200 and about 1300, inclusive, of Figure 5 (SEQ ID NO:7). Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209917

(DNA21624-1391), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209917 (DNA21624-1391).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 367, inclusive of Figure 6 (SEQ ID NO:8), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO189 polypeptide having the sequence of amino acid residues from about 1 to about 367, inclusive of Figure 6 (SEQ ID NO:8), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 367, inclusive of Figure 6 (SEQ ID NO:8), or (b) the complement of the DNA of (a).

20 In another embodiment, the invention provides isolated PRO189 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO189 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 367 of Figure 6 (SEQ ID NO:8).

25 In another aspect, the invention concerns an isolated PRO189 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 367, inclusive of Figure 6 (SEQ ID NO:8).

30 In a further aspect, the invention concerns an isolated PRO189 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 367 of Figure 6 (SEQ ID NO:8).

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO189 polypeptide having the sequence of amino acid residues from about 1 to about 367, inclusive of Figure 6 (SEQ ID NO:8), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising

the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO189 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO189 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO189 polypeptide, by contacting the native PRO189 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO189 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 10 4. PRO190

Applicants have identified a cDNA clone that encodes a novel polypeptide having seven transmembrane domains and having sequence identity with CMP-sialic acid and UDP-galactose transporters, wherein the polypeptide is designated in the present application as "PRO190".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO190 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO190 polypeptide having amino acid residues 1 through 424 of Figure 9 (SEQ ID NO:14), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on June 2, 1998 with the ATCC as DNA23334-1392 which includes the nucleotide sequence encoding  
20 PRO190.

In another embodiment, the invention provides isolated PRO190 polypeptide. In particular, the invention provides isolated native sequence PRO190 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 424 of Figure 9 (SEQ ID NO:14). An additional embodiment of the present invention is directed to an isolated PRO190 polypeptide, excluding the transmembrane domains.

25 Optionally, the PRO190 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on June 2, 1998 with the ATCC as DNA23334-1392.

In another embodiment, the invention provides an expressed sequence tag (EST) comprising the nucleotide sequence of SEQ ID NO:15.

#### 30 5. PRO341

A cDNA clone (DNA26288-1239) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO341".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO341 polypeptide.

35 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO341 polypeptide having

the sequence of amino acid residues from about 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20), or (b) the complement of the DNA molecule of (a).

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO341 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 380 or about 431 and about 1753, inclusive, of Figure 11 (SEQ ID NO:19). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209792 (DNA26288-1239) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209792 (DNA26288-1239).

15 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20), or (b) the complement of the DNA of (a).

20 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 165 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO341 polypeptide having the sequence of amino acid residues from 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

25 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO341 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 17 in the sequence of Figure 12 (SEQ ID NO:20). The transmembrane domains have been tentatively identified as extending from about amino acid position 171 to about amino acid position 190, from about amino acid position 220 to about amino acid position 239, from about amino acid position 259 to about amino acid position 275, from about amino acid position 286 to about amino acid position 305, from about amino acid position 316 to about amino acid position 335, from about amino acid position 353 to about amino acid position 378 and from about amino acid position 396 to about amino acid position 417 in the PRO341 amino acid sequence (Figure 12, SEQ ID NO:20).

35 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more



preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO341 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 11 (SEQ ID NO:19).

In another embodiment, the invention provides isolated PRO341 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO341 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 18 to about 458 of Figure 12 (SEQ ID NO:20).

In another aspect, the invention concerns an isolated PRO341 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20).

In a further aspect, the invention concerns an isolated PRO341 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20).

In yet another aspect, the invention concerns an isolated PRO341 polypeptide, comprising the sequence of amino acid residues 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20), or a fragment thereof sufficient to provide a binding site for an anti-PRO341 antibody. Preferably, the PRO341 fragment retains a qualitative biological activity of a native PRO341 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO341 polypeptide having the sequence of amino acid residues from about 1 or about 18 to about 458, inclusive of Figure 12 (SEQ ID NO:20), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA12920 comprising the nucleotide sequence of SEQ ID NO:21 (see Figure 13).

**6. PRO180**

A cDNA clone (DNA26843-1389) has been identified that encodes a novel polypeptide having multiple transmembrane domains designated in the present application as "PRO180".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO180 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO180 polypeptide having the sequence of amino acid residues from about 1 to about 266, inclusive of Figure 15 (SEQ ID NO:23), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO180 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 121 and about 918, inclusive, of Figure 14 (SEQ ID NO:22). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203099 (DNA26843-1389), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
20 Deposit No. 203099 (DNA26843-1389).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 266, inclusive of Figure 15 (SEQ ID  
25 NO:23), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO180 polypeptide having the sequence of amino acid residues from about 1 to about 266, inclusive of Figure 15 (SEQ ID NO:23), or (b) the complement  
30 of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO180 polypeptide in its soluble form, i.e. transmembrane domains deleted or inactivated variants, or is  
35 complementary to such encoding nucleic acid molecule. The transmembrane domains are shown in Figure 15. It is believed that PRO180 has a type II transmembrane domain from about amino acids 13-33 of SEQ ID NO:23.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 266, inclusive of Figure 15 (SEQ ID NO:23), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO180 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

10 In another embodiment, the invention provides isolated PRO180 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO180 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 266 of Figure 15 (SEQ ID NO:23).

15 In another aspect, the invention concerns an isolated PRO180 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 266, inclusive of Figure 15 (SEQ ID NO:23).

20 In a further aspect, the invention concerns an isolated PRO180 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 266 of Figure 15 (SEQ ID NO:23).

In yet another aspect, the invention concerns an isolated PRO180 polypeptide, comprising the sequence of amino acid residues 1 to about 266, inclusive of Figure 15 (SEQ ID NO:23), or a fragment thereof sufficient to provide a binding site for an anti-PRO180 antibody. Preferably, the PRO180 fragment retains a qualitative biological activity of a native PRO180 polypeptide.

25 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO180 polypeptide having the sequence of amino acid residues from about 1 to about 266, inclusive of Figure 15 (SEQ ID NO:23), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO180 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO180 antibody.

35 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO180 polypeptide, by contacting the native PRO180 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO180 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

In another embodiment, the invention provides an expressed sequence tag (EST) (DNA12922) comprising the nucleotide sequence of Figure 16 (SEQ ID NO:24).

5 7. **PRO194**

Applicants have identified a cDNA clone that encodes a novel transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO194".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO194 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO194 polypeptide having amino acid residues 1 to 264 of Figure 18 (SEQ ID NO:28), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO194 polypeptide having amino acid residues about 18 to 264 of Figure 18 (SEQ ID NO:28) or amino acid 1 or about 18 to X of Figure 18 (SEQ ID NO:28), where X is any amino acid from 96 to 105 of Figure 18 (SEQ ID NO:28), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA26844-1394 vector deposited on June 2, 1998 as ATCC 209926 which includes the nucleotide sequence encoding PRO194.

In another embodiment, the invention provides isolated PRO194 polypeptide. In particular, the invention provides isolated native sequence PRO194 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 264 of Figure 18 (SEQ ID NO:28). Additional embodiments of the present invention are directed to PRO194 polypeptides comprising amino acids about 18 to 264 of Figure 18 (SEQ ID NO:28) or amino acid 1 or about 18 to X of Figure 18 (SEQ ID NO:28), where X is any amino acid from 96 to 105 of Figure 18 (SEQ ID NO:28). Optionally, the PRO194 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA26844-1394 vector deposited on June 2, 1998 as ATCC 209926.

8. **PRO203**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity to glutathione-S-transferase, wherein the polypeptide is designated in the present application as "PRO203".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO203 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO203 polypeptide having amino acid residues 1 to 347 of Figure 20 (SEQ ID NO:30), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO203 polypeptide having amino acid residues X to 347 of Figure 20 (SEQ ID NO:30), where X is any amino acid from 83 to 92 of Figure 20 (SEQ ID NO:30), or is complementary to such encoding nucleic acid sequence, and



remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA30862-1396 vector deposited on June 2, 1998, as ATCC 209920 which includes the nucleotide sequence encoding PRO203.

In another embodiment, the invention provides isolated PRO203 polypeptide. In particular, the invention provides isolated native sequence PRO203 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 347 of Figure 20 (SEQ ID NO:30). Additional embodiments of the present invention are directed to PRO203 polypeptides comprising amino acid X to 347 of Figure 20 (SEQ ID NO:30), where X is any amino acid from 83 to 92 of Figure 20 (SEQ ID NO:30). Optionally, the PRO203 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA30862-1396 vector deposited on June 2, 1998, as ATCC 209920.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA15618 which comprises the nucleotide sequence of Figure 21 (SEQ ID NO:31).

#### 9. PRO290

A cDNA clone (DNA35680-1212) has been identified which encodes a polypeptide designated in the present application as "PRO290." PRO290 polypeptides have sequence identity with NTII-1, FAN and beige.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO290 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO290 polypeptide having the sequence of amino acid residues from about 1 to about 1003, inclusive of Figure 23 (SEQ ID NO:33), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO290 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 293 and about 3301, inclusive, of Figure 22 (SEQ ID NO:32). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209790 (DNA35680-1212), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209790 (DNA35680-1212).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 1003, inclusive of Figure 23 (SEQ ID

NO:33), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO290 polypeptide having the sequence of amino acid residues from about 1 to about 1003, inclusive of Figure 23 (SEQ ID NO:33), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 1003, inclusive of Figure 23 (SEQ ID NO:33), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO290 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO290 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 1003 of Figure 23 (SEQ ID NO:33).

In another aspect, the invention concerns an isolated PRO290 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 1003, inclusive of Figure 23 (SEQ ID NO:33).

In a further aspect, the invention concerns an isolated PRO290 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 1003 of Figure 23 (SEQ ID NO:33).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO290 polypeptide having the sequence of amino acid residues from about 1 to about 1003, inclusive of Figure 23 (SEQ ID NO:33), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO290 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO290 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO290 polypeptide, by contacting the native PRO290 polypeptide with a candidate molecule and

monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO290 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 10. PRO874

Applicants have identified a cDNA clone that encodes a novel multi-span transmembrane polypeptide, which is designated in the present application as "PRO874".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO874 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO874 polypeptide having amino acid residues 1 to 321 of Figure 25 (SEQ ID NO:36), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO874 polypeptide having amino acid from about X to 321 of Figure 25 (SEQ ID NO:36), where X is any amino acid from about 270 to about 279 of Figure 25 (SEQ ID NO:36), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA40621-1440 vector deposited on June 2, 1998, as ATCC 209922 which includes the nucleotide sequence encoding PRO874.

In another embodiment, the invention provides isolated PRO874 polypeptide. In particular, the invention provides isolated native sequence PRO874 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 321 of Figure 25 (SEQ ID NO:36). Additional embodiments of the present invention are directed to PRO874 polypeptides comprising amino acids X to 321 of Figure 25 (SEQ ID NO:36), where X is any amino acid from about 270 to about 279 of Figure 25 (SEQ ID NO:36). Optionally, the PRO874 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA40621-1440 vector deposited on June 2, 1998, as ATCC 209922.

#### 11. PRO710

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to CDC45 protein, wherein the polypeptide is designated in the present application as "PRO710".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO710 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO710 polypeptide having amino acid residues 1 to 566 of Figure 27 (SEQ ID NO:41), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO710 polypeptide having amino acid residues about 33 to 566 of Figure 27 (SEQ ID NO:41) or amino acid 1 or about 33 to X of Figure 27 (SEQ ID NO:41), where X is any amino acid from 449 to 458 of Figure 27 (SEQ ID NO:41), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA44161-1434 vector deposited on May 27, 1998 as ATCC 209907 which



includes the nucleotide sequence encoding PRO710.

In another embodiment, the invention provides isolated PRO710 polypeptide. In particular, the invention provides isolated native sequence PRO710 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 566 of Figure 27 (SEQ ID NO:41). Additional embodiments of the present invention are directed to PRO710 polypeptides comprising amino acids about 33 to 566 of Figure 27 (SEQ ID NO:41) or amino acid 1 or about 33 to X of Figure 27 (SEQ ID NO:41), where X is any amino acid from 449 to 458 of Figure 27 (SEQ ID NO:41). Optionally, the PRO710 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA44161-1434 vector deposited on May 27, 1998 as ATCC 209907.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA38190 comprising the nucleotide sequence of Figure 28 (SEQ ID NO:42).

## 12. PRO1151

A cDNA clone (DNA44694-1500) has been identified, having homology to nucleic acid encoding C1q protein, that encodes a novel polypeptide, designated in the present application as "PRO1151".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1151 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1151 polypeptide having the sequence of amino acid residues from about 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1151 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 272 or about 332 and about 1048, inclusive, of Figure 29 (SEQ ID NO:46). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203114 (DNA44694-1500) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203114 (DNA44694-1500).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47), or (b) the complement of the DNA of (a).



In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1151 polypeptide having the sequence of amino acid residues from 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1151 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 20 in the sequence of Figure 30 (SEQ ID NO:47).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80 % positives, preferably at least about 85 % positives, more preferably at least about 90 % positives, most preferably at least about 95 % positives when compared with the amino acid sequence of residues 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1151 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 29 (SEQ ID NO:46).

In another embodiment, the invention provides isolated PRO1151 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1151 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 21 to about 259 of Figure 30 (SEQ ID NO:47).

In another aspect, the invention concerns an isolated PRO1151 polypeptide, comprising an amino acid sequence having at least about 80 % sequence identity, preferably at least about 85 % sequence identity, more preferably at least about 90 % sequence identity, most preferably at least about 95 % sequence identity to the sequence of amino acid residues 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47).

In a further aspect, the invention concerns an isolated PRO1151 polypeptide, comprising an amino acid sequence scoring at least about 80 % positives, preferably at least about 85 % positives, more preferably at least about 90 % positives, most preferably at least about 95 % positives when compared with the amino acid sequence of residues 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47).

In yet another aspect, the invention concerns an isolated PRO1151 polypeptide, comprising the sequence of amino acid residues 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47), or a fragment thereof sufficient to provide a binding site for an anti-PRO1151 antibody. Preferably, the PRO1151 fragment

retains a qualitative biological activity of a native PRO1151 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1151 polypeptide having the sequence of amino acid residues from about 1 or about 21 to about 259, inclusive of Figure 30 (SEQ ID NO:47), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1151 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1151 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1151 polypeptide by contacting the native PRO1151 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1151 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 13. PRO1282

A cDNA clone (DNA45495-1550) has been identified that encodes a novel polypeptide having sequence identity with leucine rich repeat proteins and designated in the present application as "PRO1282."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1282 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1282 polypeptide having the sequence of amino acid residues from about 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1282 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 189 and about 2138, inclusive, of Figure 31 (SEQ ID NO:51). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203156 (DNA45495-1550), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203156 (DNA45495-1550).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52), or the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1282 polypeptide having the sequence of amino acid residues from about 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably  
10 at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1282 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding  
15 nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 23 in the sequence of Figure 32 (SEQ ID NO:52). The transmembrane domain has been tentatively identified as extending from about amino acid position 579 through about amino acid position 599 in the PRO1282 amino acid sequence (Figure 32, SEQ ID NO:52).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA  
20 encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1282 polypeptide coding sequence that may find  
25 use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1282 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

30 In a specific aspect, the invention provides isolated native sequence PRO1282 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 24 through 673 of Figure 32 (SEQ ID NO:52).

In another aspect, the invention concerns an isolated PRO1282 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more  
35 preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52).



In a further aspect, the invention concerns an isolated PRO1282 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 24 through 673 of Figure 32 (SEQ ID NO:52).

5 In yet another aspect, the invention concerns an isolated PRO1282 polypeptide, comprising the sequence of amino acid residues 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52), or a fragment thereof sufficient to provide a binding site for an anti-PRO1282 antibody. Preferably, the PRO1282 fragment retains a qualitative biological activity of a native PRO1282 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1282 polypeptide having the sequence of amino acid residues from about 24 to about 673, inclusive of Figure 32 (SEQ ID NO:52), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the  
15 polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1282 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1282 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1282 polypeptide, by contacting the native PRO1282 polypeptide with a candidate molecule and  
20 monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1282 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 14. **PRO358**

25 Applicants have identified a novel cDNA clone that encodes novel human Toll polypeptides, designated in the present application as PRO358.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising a DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to (a) a DNA molecule encoding a PRO358 polypeptide having amino acids 20 to 575 of Figure 34 (SEQ ID NO:57), or (b) the complement of the DNA molecule of (a). The complementary DNA molecule preferably remains stably bound to such encoding nucleic acid sequence under at least moderate, and optionally, under high stringency conditions.

In a further embodiment, the isolated nucleic acid molecule comprises a polynucleotide that has at least  
35 about 90%, preferably at least about 95% sequence identity with a polynucleotide encoding a polypeptide comprising the sequence of amino acids 1 to 811 of Figure 34 (SEQ ID NO:57).



In a specific embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding native or variant PRO358 polypeptide, with or without the N-terminal signal sequence, and with or without the transmembrane regions of the respective full-length sequences. In one aspect, the isolated nucleic acid comprises DNA encoding a mature, full-length native PRO358 polypeptide having amino acid residues 1 to 811 of Figure 34 (SEQ ID NO:57), or is complementary to such encoding nucleic acid sequence. In another aspect, the invention concerns an isolated nucleic acid molecule that comprises DNA encoding a native PRO358 polypeptide without an N-terminal signal sequence, or is complementary to such encoding nucleic acid sequence. In yet another embodiment, the invention concerns nucleic acid encoding transmembrane-domain deleted or inactivated forms of the full-length native PRO358 protein.

10 In another embodiment, the invention provides an isolated nucleic acid molecule which comprises the clone (DNA 47361-1249) deposited on November 7, 1997, under ATCC number 209431.

15 In a specific embodiment, the invention provides a vector comprising a polynucleotide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity with a polynucleotide encoding a polypeptide comprising the sequence of amino acids 20 to 811 of Figure 34 (SEQ ID NO:57), or the complement of such polynucleotide. In a particular embodiment, the vector comprises DNA encoding the novel Toll homologue (PRO358), with or without the N-terminal signal sequence (about amino acids 1 to 19), or a transmembrane-domain (about amino acids 576-595) deleted or inactivated variant thereof, or the extracellular domain (about amino acids 20 to 595) of the mature protein, or a protein comprising any one of these sequences. A host cell comprising such a vector is also provided.

20 In another embodiment, the invention provides isolated PRO358 polypeptides. The invention further provides an isolated native sequence PRO358 polypeptide, or variants thereof. In particular, the invention provides an isolated native sequence PRO358 polypeptide, which in certain embodiments, includes the amino acid sequence comprising residues 20 to 575, or 20 to 811, or 1 to 811 of Figure 34 (SEQ ID NO:57).

25 In yet another embodiment, the invention concerns agonists and antagonists of the native PRO358 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO358 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of the native PRO358 polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO358 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

30 The invention further concerns a composition comprising an antibody specifically binding a PRO358 polypeptide, in combination with a pharmaceutically acceptable carrier.

The invention also concerns a method of treating septic shock comprising administering to a patient an effective amount of an antagonist of a PRO358 polypeptide. In a specific embodiment, the antagonist is a blocking antibody specifically binding a native PRO358 polypeptide.

35

**15.     PRO1310**

A cDNA clone (DNA47394-1572) has been identified that encodes a novel polypeptide having sequence identity with carboxypeptidase X2 and designated in the present application as "PRO1310."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1310 polypeptide.

5         In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1310 polypeptide having the sequence of amino acid residues from about 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62), or (b) the complement of the DNA molecule of (a).

10         In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1310 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 401 and about 2593, inclusive, of Figures 35A-B (SEQ ID NO:61). Preferably, hybridization occurs under stringent hybridization and wash conditions.

15         In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203109 (DNA47394-1572), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
20     Deposit No. 203109 (DNA47394-1572).

25         In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62), or the complement of the DNA of (a).

30         In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1310 polypeptide having the sequence of amino acid residues from about 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35         In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1310 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1310 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 26 through 765 of Figure 36 (SEQ ID NO:62).

5 In another aspect, the invention concerns an isolated PRO1310 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62).

10 In a further aspect, the invention concerns an isolated PRO1310 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 26 through 765 of Figure 36 (SEQ ID NO:62).

15 In yet another aspect, the invention concerns an isolated PRO1310 polypeptide, comprising the sequence of amino acid residues 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62), or a fragment thereof sufficient to provide a binding site for an anti-PRO1310 antibody. Preferably, the PRO1310 fragment retains a qualitative biological activity of a native PRO1310 polypeptide.

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1310 polypeptide having the sequence of amino acid residues from about 26 to about 765, inclusive of Figure 36 (SEQ ID NO:62), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

25 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1310 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1310 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1310 polypeptide, by contacting the native PRO1310 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

30 In a still further embodiment, the invention concerns a composition comprising a PRO1310 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 16. PRO698

35 Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to olfactomedin, wherein the polypeptide is designated in the present application as "PRO698".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO698 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO698



polypeptide having amino acid residues 1 to 510 of Figure 38 (SEQ ID NO:67), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO698 polypeptide having amino acid residues about 21 to 510 of Figure 38 (SEQ ID NO:67), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48320-1433 vector deposited on May 27, 1998 as ATCC 209904 which includes the nucleotide sequence encoding PRO698.

In another embodiment, the invention provides isolated PRO698 polypeptide. In particular, the invention provides isolated native sequence PRO698 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 510 of Figure 38 (SEQ ID NO:67). Additional embodiments of the present invention are directed to PRO698 polypeptides comprising amino acids about 21 to 510 of Figure 38 (SEQ ID NO:67). Optionally, the PRO698 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48320-1433 vector deposited on May 27, 1998 as ATCC 209904.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA39906 comprising the nucleotide sequence of Figure 39 (SEQ ID NO:68).

#### 17. PRO732

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to the human placental protein Diff33, wherein the polypeptide is designated in the present application as "PRO732".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO732 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO732 polypeptide having amino acid residues 1 to 453 of Figure 41 (SEQ ID NO:73), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO732 polypeptide having amino acid residues about 29 to 453 of Figure 41 (SEQ ID NO:73) or amino acid 1 or about 29 to X of Figure 41 (SEQ ID NO:73), where X is any amino acid from 31 to 40 of Figure 41 (SEQ ID NO:73), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA48334-1435 vector deposited on June 2, 1998 as ATCC 209924 which includes the nucleotide sequence encoding PRO732.

In another embodiment, the invention provides isolated PRO732 polypeptide. In particular, the invention provides isolated native sequence PRO732 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 453 of Figure 41 (SEQ ID NO:73). Additional embodiments of the present invention are directed to PRO732 polypeptides comprising amino acids about 29 to 453 of Figure 41 (SEQ ID NO:73) or amino acid 1 or about 29 to X of Figure 41 (SEQ ID NO:73), where X is any amino acid from 31 to 40 of Figure 41 (SEQ ID NO:73). Optionally, the PRO732 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA48334-1435 vector deposited on June 2,



1998 as ATCC 209924.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA20239 comprising the nucleotide sequence of Figure 42 (SEQ ID NO:74).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA38050 comprising the nucleotide sequence of Figure 43 (SEQ ID NO:75).

5 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA40683 comprising the nucleotide sequence of Figure 44 (SEQ ID NO:76).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA42580 comprising the nucleotide sequence of Figure 45 (SEQ ID NO:77).

## 10 18. PRO1120

A cDNA clone (DNA48606-1479) has been identified that encodes a novel polypeptide having homology sulfatases, designated in the present application as "PRO1120."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1120 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1120 polypeptide having the sequence of amino acid residues from about 18 to about 867, inclusive of Figure 47 (SEQ ID NO:84), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1120 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 659 and about 3208, inclusive, of Figures 46A-B (SEQ ID NO:83). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203040 (DNA48606-1479), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
30 Deposit No. 203040 (DNA48606-1479).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 18 to about 867, inclusive of Figure 47 (SEQ ID  
35 NO:84), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under

stringent conditions with (a) a DNA molecule encoding a PRO1120 polypeptide having the sequence of amino acid residues from about 18 to about 867, inclusive of Figure 47 (SEQ ID NO:84), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1120 polypeptide, with or without the N-terminal signal sequence, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 17 in the sequence of Figure 47 (SEQ ID NO:84).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 18 to about 867, inclusive of Figure 47 (SEQ ID NO:84), or (b) the complement of the DNA of (a).

15 Another embodiment is directed to fragments of a PRO1120 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1120 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

20 In a specific aspect, the invention provides isolated native sequence PRO1120 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 18 to 867 of Figure 47 (SEQ ID NO:84).

25 In another aspect, the invention concerns an isolated PRO1120 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 18 to about 867, inclusive of Figure 47 (SEQ ID NO:84).

In a further aspect, the invention concerns an isolated PRO1120 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 18 to 867 of Figure 47 (SEQ ID NO:84).

30 In yet another aspect, the invention concerns an isolated PRO1120 polypeptide, comprising the sequence of amino acid residues 18 to about 867, inclusive of Figure 47 (SEQ ID NO:84), or a fragment thereof sufficient to provide a binding site for an anti-PRO1120 antibody. Preferably, the PRO1120 fragment retains a qualitative biological activity of a native PRO1120 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1120 polypeptide having the sequence of amino acid residues from about 18 to about 867, inclusive of Figure 47 (SEQ ID NO:84), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence

identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

5 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1120 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1120 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1120 polypeptide, by contacting the native PRO1120 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

10 In a still further embodiment, the invention concerns a composition comprising a PRO1120 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 19. PRO537

A cDNA clone (DNA49141-1431) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO537".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO537 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO537 polypeptide having  
20 the sequence of amino acid residues from about 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO537 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 97 or about 190 and about 441, inclusive, of Figure 48 (SEQ ID NO:94). Preferably, hybridization occurs under  
25 stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203003  
30 (DNA49141-1431) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203003 (DNA49141-1431).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
35 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95), or (b) the complement of the DNA of (a).



In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO537 polypeptide having the sequence of amino acid residues from 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO537 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 31 in the sequence of Figure 49 (SEQ ID NO:95).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO537 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 48 (SEQ ID NO:94).

In another embodiment, the invention provides isolated PRO537 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO537 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 32 to about 115 of Figure 49 (SEQ ID NO:95).

In another aspect, the invention concerns an isolated PRO537 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95).

In a further aspect, the invention concerns an isolated PRO537 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95).

In yet another aspect, the invention concerns an isolated PRO537 polypeptide, comprising the sequence of amino acid residues 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95), or a fragment thereof sufficient to provide a binding site for an anti-PRO537 antibody. Preferably, the PRO537 fragment



retains a qualitative biological activity of a native PRO537 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO537 polypeptide having the sequence of amino acid residues from about 1 or about 32 to about 115, inclusive of Figure 49 (SEQ ID NO:95), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

## 10 20. PRO536

A cDNA clone (DNA49142-1430) has been identified, that encodes a novel secreted polypeptide, designated in the present application as "PRO536".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO536 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO536 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO536 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 48 or about 123 and about 986, inclusive, of Figure 50 (SEQ ID NO:96). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203002 (DNA49142-1430) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
30 ATCC Deposit No. 203002 (DNA49142-1430).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID  
35 NO:97), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA

molecule encoding a PRO536 polypeptide having the sequence of amino acid residues from 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO536 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 25 in the sequence of Figure 51 (SEQ ID NO:97).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97), or (b) the complement of the DNA of (a).

15 Another embodiment is directed to fragments of a PRO536 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 50 (SEQ ID NO:96).

20 In another embodiment, the invention provides isolated PRO536 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO536 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 26 to about 313 of Figure 51 (SEQ ID NO:97).

25 In another aspect, the invention concerns an isolated PRO536 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97).

30 In a further aspect, the invention concerns an isolated PRO536 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97).

35 In yet another aspect, the invention concerns an isolated PRO536 polypeptide, comprising the sequence of amino acid residues 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97), or a fragment thereof sufficient to provide a binding site for an anti-PRO536 antibody. Preferably, the PRO536 fragment retains a qualitative biological activity of a native PRO536 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO536 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 313, inclusive of Figure 51 (SEQ ID NO:97), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

21. **PRO535**

10 A cDNA clone (DNA49143-1429) has been identified, having homology to nucleic acid encoding a putative peptidyl-prolyl isomerase that encodes a novel polypeptide, designated in the present application as "PRO535".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO535 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO535 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO535 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 78 or about 153 and about 680, inclusive, of Figure 52 (SEQ ID NO:98). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203013 (DNA49143-1429) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
30 ATCC Deposit No. 203013 (DNA49143-1429).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID  
35 NO:99), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA



molecule encoding a PRO535 polypeptide having the sequence of amino acid residues from 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO535 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 25 in the sequence of Figure 53 (SEQ ID NO:99). The transmembrane  
10 domain has been tentatively identified as extending from about amino acid position 155 to about amino acid position 174 in the PRO535 amino acid sequence (Figure 53, SEQ ID NO:99).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
15 amino acid sequence of residues 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO535 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
20 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 52 (SEQ ID NO:98).

In another embodiment, the invention provides isolated PRO535 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

25 In a specific aspect, the invention provides isolated native sequence PRO535 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 26 to about 201 of Figure 53 (SEQ ID NO:99).

In another aspect, the invention concerns an isolated PRO535 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the  
30 sequence of amino acid residues 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99).

In a further aspect, the invention concerns an isolated PRO535 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99).

35 In yet another aspect, the invention concerns an isolated PRO535 polypeptide, comprising the sequence of amino acid residues 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99), or a fragment thereof sufficient to provide a binding site for an anti-PRO535 antibody. Preferably, the PRO535 fragment



retains a qualitative biological activity of a native PRO535 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO535 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 201, inclusive of Figure 53 (SEQ ID NO:99), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO535 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO535 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO535 polypeptide by contacting the native PRO535 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO535 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA30861 comprising the nucleotide sequence of Figure 54 (SEQ ID NO:100).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA36351 comprising the nucleotide sequence of Figure 55 (SEQ ID NO:101).

## 22. PRO718

Applicants have identified a cDNA clone that encodes a novel tetraspan membrane polypeptide, wherein the polypeptide is designated in the present application as "PRO718".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO718 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO718 polypeptide having amino acid residues 1 to 157 of Figure 57 (SEQ ID NO:103), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO718 polypeptide having amino acid residues X to 157 of Figure 57 (SEQ ID NO:103), where X is any amino acid from 143 to 152 of Figure 57 (SEQ ID NO:103), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49647-1398 vector deposited on June 2, 1998 as ATCC 209919 which includes the nucleotide sequence encoding PRO718.

In another embodiment, the invention provides isolated PRO718 polypeptide. In particular, the invention provides isolated native sequence PRO718 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 157 of Figure 57 (SEQ ID NO:103). Additional embodiments of the present invention are directed to isolated PRO718 polypeptides comprising amino acids X to 157 of Figure 57

(SEQ ID NO:103), where X is any amino acid from 143 to 152 of Figure 57 (SEQ ID NO:103). Optionally, the PRO718 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49647-1398 vector deposited on June 2, 1998 as ATCC 209919.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA15386 which comprises the nucleotide sequence of Figure 58 (SEQ ID NO:104).

5 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA16630 which comprises the nucleotide sequence of Figure 59 (SEQ ID NO:105).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA16829 which comprises the nucleotide sequence of Figure 60 (SEQ ID NO:106).

10 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA28357 which comprises the nucleotide sequence of Figure 61 (SEQ ID NO:107).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA43512 which comprises the nucleotide sequence of Figure 62 (SEQ ID NO:108).

### 23. PRO872

15 Applicants have identified a cDNA clone, DNA49819-1439, that encodes a novel polypeptide having homology to dehydrogenases wherein the polypeptide is designated in the present application as "PRO872".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO872 polypeptide.

20 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO872 polypeptide having the sequence of amino acid residues from 1 or about 19 to about 610, inclusive of Figure 64 (SEQ ID NO:113), or (b) the complement of the DNA molecule of (a).

25 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO872 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid between about residues 68 and about 1843, inclusive of Figure 63 (SEQ ID NO:112). Preferably, hybridization occurs under stringent hybridization and wash conditions.

30 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209931 (DNA49819-1439), which was deposited on June 2, 1998. In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209931 (DNA49819-1439).

35 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence

identity to the sequence of amino acid residues 1 or about 19 to about 610, inclusive of Figure 64 (SEQ ID NO:113).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO872 extracellular domain (ECD), with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble variants (i.e. transmembrane domain(s) deleted or inactivated) or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 to about amino acid position 18 in the sequence of Figure 64 (SEQ ID NO:113). The first transmembrane domain region has been tentatively identified as extending from about amino acid position 70 to about amino acid position 87 in the PRO872 amino acid sequence (Figure 64, SEQ ID NO:113).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 19 to about 610, inclusive of Figure 64 (SEQ ID NO:113).

Another embodiment is directed to fragments of a PRO872 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO872 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO872 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 19 to 610 of Figure 64 (SEQ ID NO:113).

In another aspect, the invention concerns an isolated PRO872 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 19 to 610, inclusive of Figure 64 (SEQ ID NO:113).

In a further aspect, the invention concerns an isolated PRO872 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 19 to 610 of Figure 64 (SEQ ID NO:113).

In another aspect, the invention concerns a PRO872 extracellular domain comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 19 to X of Figure 64 (SEQ ID NO:113), wherein X is any one of amino acid residues 66 to 75 of Figure 64 (SEQ ID NO:113).

In yet another aspect, the invention concerns an isolated PRO872 polypeptide, comprising the sequence of amino acid residues 1 or about 19 to about 610, inclusive of Figure 64 (SEQ ID NO:113), or a fragment thereof sufficient to provide a binding site for an anti-PRO872 antibody. Preferably, the PRO872 fragment

retains a qualitative biological activity of a native PRO872 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO872 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

In yet another embodiment, the invention concerns agonist and antagonists of the PRO872 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO872 antibody.

5 In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO872 polypeptide.

In still a further embodiment, the invention concerns a composition comprising a PRO872 polypeptide as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 10 24. PRO1063

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to human type IV collagenase, wherein the polypeptide is designated in the present application as "PRO1063".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1063 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1063 polypeptide having amino acid residues 1 to 301 of Figure 66 (SEQ ID NO:115), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1063 polypeptide having amino acid residues about 22 to 301 of Figure 66 (SEQ ID NO:115), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally,  
20 under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA49820-1427 vector deposited on June 2, 1998 as ATCC 209932 which includes the nucleotide sequence encoding PRO1063.

25 In another embodiment, the invention provides isolated PRO1063 polypeptide. In particular, the invention provides isolated native sequence PRO1063 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 301 of Figure 66 (SEQ ID NO:115). Additional embodiments of the present invention are directed to PRO1063 polypeptides comprising amino acids about 22 to 301 of Figure 66 (SEQ ID NO:115). Optionally, the PRO1063 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA49820-1427 vector deposited on June 2, 1998 as ATCC 209932.

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#### 25. PRO619

A cDNA clone (DNA49821-1562) has been identified that encodes a novel polypeptide, designated in the present application as "PRO619." PRO619 polypeptides have sequence identity with VpreB genes, particularly to VpreB3.

35 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO619 polypeptide.



In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO619 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 123, inclusive of Figure 68 (SEQ ID NO:117), or (b) the complement of the DNA molecule of (a).

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO619 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 81 or 141 and about 449, inclusive, of Figure 67 (SEQ ID NO:116). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209981 (DNA49821-1562), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
15 Deposit No. 209981 (DNA49821-1562).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 21 to about 123, inclusive of Figure 68 (SEQ  
20 ID NO:117), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO619 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 123, inclusive of Figure 68 (SEQ ID NO:117), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an  
25 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO619 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, which  
30 is in a soluble form. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 20 in the sequence of Figure 68 (SEQ ID NO:117).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
35 amino acid sequence of residues 1 or 21 to about 123, inclusive of Figure 68 (SEQ ID NO:117), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO619 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 40 through about 80 nucleotides in length, preferably from about 20 through about 60 nucleotides in length, more preferably from about 20 through about 50 nucleotides in length, and most preferably from about 20 through about 40 nucleotides in length.

5 In another embodiment, the invention provides isolated PRO619 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO619 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 21 through 123 of Figure 68 (SEQ ID NO:117).

10 In another aspect, the invention concerns an isolated PRO619 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 21 through about 123, inclusive of Figure 68 (SEQ ID NO:117).

15 In a further aspect, the invention concerns an isolated PRO619 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 21 through 123 of Figure 68 (SEQ ID NO:117).

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO619 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 123, inclusive of Figure 68 (SEQ ID NO:117), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

25 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO619 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO619 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO619 polypeptide, by contacting the native PRO619 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

30 In a still further embodiment, the invention concerns a composition comprising a PRO619 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

## 26. PRO943

35 A cDNA clone (DNA52192-1369) has been identified, having homology to nucleic acid encoding fibroblast growth factor receptor-4 that encodes a novel polypeptide, designated in the present application as "PRO943".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO943 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO943 polypeptide having the sequence of amino acid residues from about 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO943 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 150 or about 201 and about 1661, inclusive, of Figure 69 (SEQ ID NO:118). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203042 (DNA52192-1369) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203042 (DNA52192-1369).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO943 polypeptide having the sequence of amino acid residues from 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO943 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 17 in the sequence of Figure 70 (SEQ ID NO:119). The transmembrane domain has been tentatively identified as extending from about amino acid position 376 to about amino acid position 396 in the PRO943 amino acid sequence (Figure 70, SEQ ID NO:119).



In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO943 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 69 (SEQ ID NO:118).

10 In another embodiment, the invention provides isolated PRO943 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO943 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 18 to about 504 of Figure 70 (SEQ ID NO:119).

15 In another aspect, the invention concerns an isolated PRO943 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119).

20 In a further aspect, the invention concerns an isolated PRO943 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119).

25 In yet another aspect, the invention concerns an isolated PRO943 polypeptide, comprising the sequence of amino acid residues 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119), or a fragment thereof sufficient to provide a binding site for an anti-PRO943 antibody. Preferably, the PRO943 fragment retains a qualitative biological activity of a native PRO943 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO943 polypeptide having the sequence of amino acid residues from about 1 or about 18 to about 504, inclusive of Figure 70 (SEQ ID NO:119), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO943 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO943 antibody.



In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO943 polypeptide by contacting the native PRO943 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO943 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

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27. **PRO1188**

A cDNA clone (DNA52598-1518) has been identified that encodes a novel polypeptide having homology to nucleotide pyrophosphohydrolase and designated in the present application as "PRO1188."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1188 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1188 polypeptide having the sequence of amino acid residues from about 22 to about 1184, inclusive of Figure 72 (SEQ ID NO:124), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1188 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 199 and about 3687, inclusive, of Figure 71 (SEQ ID NO:123). Preferably, hybridization occurs under stringent hybridization and wash conditions.

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In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203107 (DNA52598-1518), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
25 Deposit No. 203107 (DNA52598-1518).

25

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 22 to about 1184, inclusive of Figure 72 (SEQ ID NO:124), or the complement of the DNA of (a).

30

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1188 polypeptide having the sequence of  
35 amino acid residues from about 22 to about 1184, inclusive of Figure 72 (SEQ ID NO:124), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most

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preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1188 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 21 in the sequence of Figure 72 (SEQ ID NO:124).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 22 to about 1184, inclusive of Figure 72 (SEQ ID NO:124), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1188 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1188 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 22 to 1184 of Figure 72 (SEQ ID NO:124).

In another aspect, the invention concerns an isolated PRO1188 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 22 to about 1184, inclusive of Figure 72 (SEQ ID NO:124).

In a further aspect, the invention concerns an isolated PRO1188 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 22 to 1184 of Figure 72 (SEQ ID NO:124).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1188 polypeptide having the sequence of amino acid residues from about 22 to about 1184, inclusive of Figure 72 (SEQ ID NO:124), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1188 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1188 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1188 polypeptide, by contacting the native PRO1188 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1188 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**28. PRO1133**

A cDNA clone (DNA53913-1490) has been identified that encodes a novel polypeptide having sequence identity with netrin-1a and designated in the present application as "PRO1133."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1133 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1133 polypeptide having the sequence of amino acid residues from about 19 to about 438, inclusive of Figure 74 (SEQ ID NO:129), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1133 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 320 and about 1579, inclusive, of Figure 73 (SEQ ID NO:128). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203162 (DNA53913-1490), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
20 Deposit No. 203162 (DNA53913-1490).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 19 to about 438, inclusive of Figure 74 (SEQ ID  
25 NO:129), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1133 polypeptide having the sequence of amino acid residues from about 19 to about 438, inclusive of Figure 74 (SEQ ID NO:129), or (b) the  
30 complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more  
35 preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 19 to about 438, inclusive of Figure 74 (SEQ ID NO:129), or (b) the complement of the DNA of (a).



Another embodiment is directed to fragments of a PRO1133 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

5 In another embodiment, the invention provides isolated PRO1133 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1133 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 19 through 438 of Figure 74 (SEQ ID NO:129).

10 In another aspect, the invention concerns an isolated PRO1133 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 19 to about 438, inclusive of Figure 74 (SEQ ID NO:129).

15 In a further aspect, the invention concerns an isolated PRO1133 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 19 through 438 of Figure 74 (SEQ ID NO:129).

20 In yet another aspect, the invention concerns an isolated PRO1133 polypeptide, comprising the sequence of amino acid residues 19 to about 438, inclusive of Figure 74 (SEQ ID NO:129), or a fragment thereof sufficient to provide a binding site for an anti-PRO1133 antibody. Preferably, the PRO1133 fragment retains a qualitative biological activity of a native PRO1133 polypeptide.

25 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1133 polypeptide having the sequence of amino acid residues from about 19 to about 438, inclusive of Figure 74 (SEQ ID NO:129), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

30 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1133 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1133 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1133 polypeptide, by contacting the native PRO1133 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

35 In a still further embodiment, the invention concerns a composition comprising a PRO1133 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.



**29. PRO784**

A cDNA clone (DNA53978-1443) has been identified that encodes a novel polypeptide, designated in the present application as "PRO784".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO784 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO784 polypeptide having the sequence of amino acid residues from about 16 to about 228, inclusive of Figure 76 (SEQ ID NO:135), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO784 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 182 and about 820, inclusive, of Figure 75 (SEQ ID NO:134). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209983 (DNA53978-1443), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
20 Deposit No. 209983 (DNA53978-1443).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 16 to about 228, inclusive of Figure 76 (SEQ ID  
25 NO:135), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 50, and preferably at least 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO784 polypeptide having the sequence of amino acid residues from about 16 to about 228, inclusive of Figure 76 (SEQ ID NO:135), or (b) the complement of the DNA molecule  
30 of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO784 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its  
35 soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position about 1 to about amino acid position 15 in the sequence of Figure 76 (SEQ ID NO: 135). The first transmembrane

domain has been tentatively identified as extending from about amino acid position 68 to about amino acid position 87 in the PRO784 amino acid sequence (Figure 76, SEQ ID NO:135).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 16 to about 228, inclusive of Figure 76 (SEQ ID NO:135), or (b) the complement of the DNA of (a).

In another aspect, the invention concerns hybridization probes that comprise fragments of the PRO784 coding sequence, or complementary sequence thereof. The hybridization probes preferably have at least about 20 nucleotides to about 80 nucleotides, and more preferably, at least about 40 to about 80 nucleotides.

10 In another embodiment, the invention provides isolated PRO784 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO784 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 16 to 228 of Figure 76 (SEQ ID NO:135).

15 In another aspect, the invention concerns an isolated PRO784 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 16 to about 228, inclusive of Figure 76 (SEQ ID NO:135).

20 In a further aspect, the invention concerns an isolated PRO784 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 16 to 228 of Figure 76 (SEQ ID NO:135).

25 In yet another aspect, the invention concerns an isolated PRO784 polypeptide, comprising the sequence of amino acid residues 16 to about 228, inclusive of Figure 76 (SEQ ID NO:135), or a fragment thereof sufficient to provide a binding site for an anti-PRO784 antibody. Preferably, the PRO784 fragment retains a qualitative biological activity of a native PRO784 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO784 polypeptide having the sequence of amino acid residues from about 16 to about 228, inclusive of Figure 76 (SEQ ID NO:135), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO784 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO784 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO784 polypeptide, by contacting the native PRO784 polypeptide with a candidate molecule and

monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO784 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

30. **PRO783**

5 Applicants have identified a cDNA clone that encodes a novel multi-span transmembrane polypeptide, wherein the polypeptide is designated in the present application as "PRO783".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO783 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO783 polypeptide having amino acid residues 1 to 489 of Figure 79 (SEQ ID NO:138), or is complementary to such  
10 encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO783 polypeptide having amino acid residues 1 to X of Figure 79 (SEQ ID NO:138), where X is any amino acid from 19 to 28 of Figure 79 (SEQ ID NO:138), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The  
15 isolated nucleic acid sequence may comprise the cDNA insert of the DNA53996-1442 vector deposited on June 2, 1998 as ATCC 209921 which includes the nucleotide sequence encoding PRO783.

In another embodiment, the invention provides isolated PRO783 polypeptide. In particular, the invention provides isolated native sequence PRO783 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 489 of Figure 79 (SEQ ID NO:138). Additional embodiments of the  
20 present invention are directed to PRO783 polypeptides comprising amino acid 1 to about X of Figure 79 (SEQ ID NO:138), where X is any amino acid from 19 to 28 of Figure 79 (SEQ ID NO:138). Optionally, the PRO783 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA53996-1442 vector deposited on June 2, 1998, as ATCC 209921.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as  
25 DNA45201 which comprises the nucleic acid sequence shown in Figure 80 (SEQ ID NO:139).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA14575 which comprises the nucleic acid sequence shown in Figure 81 (SEQ ID NO:140).

31. **PRO820**

30 A cDNA clone (DNA56041-1416) has been identified, having sequence identity with immunoglobulin gamma Fc receptors that encodes a novel polypeptide, designated in the present application as "PRO820".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO820 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO820 polypeptide having  
35 the sequence of amino acid residues from about 1 or 16 to about 124, inclusive of Figure 83 (SEQ ID NO:146),

or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-124, or in another embodiment, 16-124.

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO820 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 115 or 160 and about 486, inclusive, of Figure 82 (SEQ ID NO:145). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203021 (DNA56041-1416), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. (DNA56041-1416).

15 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 16 to about 124, inclusive of Figure 83 (SEQ ID NO:146), or the complement of the DNA of (a).

20 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO820 polypeptide having the sequence of amino acid residues from about 1 or 16 to about 124, inclusive of Figure 83 (SEQ ID NO:146), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

25 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 16 to about 124, inclusive of Figure 83 (SEQ ID NO:146), or (b) the complement of the DNA of (a).

30 In another embodiment, the invention provides isolated PRO820 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

35 In a specific aspect, the invention provides isolated native sequence PRO820 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 16 through 124 of Figure 83 (SEQ ID NO:146).

In another aspect, the invention concerns an isolated PRO820 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more



preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 16 to about 124, inclusive of Figure 83 (SEQ ID NO:146).

In a further aspect, the invention concerns an isolated PRO820 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 16 through 124 of Figure 83 (SEQ ID NO:146).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO820 polypeptide having the sequence of amino acid residues from about 1 or 16 to about 124, inclusive of Figure 83 (SEQ ID NO:146), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO820 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO820 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO820 polypeptide, by contacting the native PRO820 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO820 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 32. PRO1080

A cDNA clone (DNA56047-1456) has been identified that encodes a novel polypeptide, designated in the present application as "PRO1080." PRO1080 polypeptides have sequence identity with DnaJ proteins.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1080 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1080 polypeptide having the sequence of amino acid residues from about 1 or 23 to about 358, inclusive of Figure 85 (SEQ ID NO:148), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-358, or in another embodiment, 23-358.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1080 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 159 or 225 and about 1232, inclusive, of Figure 84 (SEQ ID NO:147). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209948 (DNA56047-1456), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209948 (DNA56047-1456).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 23 to about 358, inclusive of Figure 85 (SEQ ID NO:148), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1080 polypeptide having the sequence of amino acid residues from about 1 or 23 to about 358, inclusive of Figure 85 (SEQ ID NO:148), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1080 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 22 in the sequence of Figure 85 (SEQ ID NO:148).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 23 to about 358, inclusive of Figure 85 (SEQ ID NO:148), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1080 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1080 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 23 through 358 of Figure 85 (SEQ ID NO:148).

In another aspect, the invention concerns an isolated PRO1080 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 23 to about 358, inclusive of Figure 85 (SEQ ID NO:148).

In a further aspect, the invention concerns an isolated PRO1080 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 23 through 358 of Figure 85 (SEQ ID NO:148).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1080 polypeptide having the sequence of amino acid residues from about 1 or 23 to about 358, inclusive of Figure 85 (SEQ ID NO:148), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1080 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1080 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1080 polypeptide, by contacting the native PRO1080 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1080 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA36527 comprising the nucleotide sequence of Figure 86 (SEQ ID NO:149).

### 33. PRO1079

A cDNA clone (DNA56050-1455) has been identified that encodes a novel polypeptide, designated in the present application as "PRO1079".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1079 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1079 polypeptide having the sequence of amino acid residues from about 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1079 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 270 and about 860, inclusive, of Figure 87 (SEQ ID NO:150). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least



about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203011 (DNA56050-1455), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203011 (DNA56050-1455).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides and preferably at least about 100 nucleotides, and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1079 polypeptide having the sequence of amino acid residues from about 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1079 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 29 in the sequence of Figure 88 (SEQ ID NO:151).

20 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151), or (b) the complement of the DNA of (a).

25 Another embodiment is directed to fragments of a PRO1079 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

30 In another embodiment, the invention provides isolated PRO1079 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1079 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 30 to 226 of Figure 88 (SEQ ID NO:151).

35 In another aspect, the invention concerns an isolated PRO1079 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151).



In a further aspect, the invention concerns an isolated PRO1079 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 30 to 226 of Figure 88 (SEQ ID NO:151).

In yet another aspect, the invention concerns an isolated PRO1079 polypeptide, comprising the sequence of amino acid residues 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151), or a fragment thereof sufficient to provide a binding site for an anti-PRO1079 antibody. Preferably, the PRO1079 fragment retains a qualitative biological activity of a native PRO1079 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1079 polypeptide having the sequence of amino acid residues from about 30 to about 226, inclusive of Figure 88 (SEQ ID NO:151), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

#### 34. PRO793

A cDNA clone (DNA56110-1437) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO793".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO793 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO793 polypeptide having the sequence of amino acid residues from about 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO793 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 77 and about 490, inclusive, of Figure 89 (SEQ ID NO:152). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203113 (DNA56110-1437) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203113 (DNA56110-1437).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153), or (b) the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO793 polypeptide having the sequence of amino acid residues from 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more  
10 preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO793 polypeptide, with or without the initiating methionine, and its soluble, i.e., transmembrane domain  
15 deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domains have been tentatively identified as extending from about amino acid position 12 to about amino acid position 30, from about amino acid position 33 to about amino acid position 52, from about amino acid position 69 to about amino acid position 89 and from about amino acid position 93 to about amino acid position 109 in the PRO793 amino acid sequence (Figure 90, SEQ ID NO:153).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA  
20 encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO793 polypeptide coding sequence that may find  
25 use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 89 (SEQ ID NO:152).

In another embodiment, the invention provides isolated PRO793 polypeptide encoded by any of the  
30 isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO793 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 to about 138 of Figure 90 (SEQ ID NO:153).

In another aspect, the invention concerns an isolated PRO793 polypeptide, comprising an amino acid  
35 sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153).

In a further aspect, the invention concerns an isolated PRO793 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153).

In yet another aspect, the invention concerns an isolated PRO793 polypeptide, comprising the sequence of amino acid residues 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153), or a fragment thereof sufficient to provide a binding site for an anti-PRO793 antibody. Preferably, the PRO793 fragment retains a qualitative biological activity of a native PRO793 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO793 polypeptide having the sequence of amino acid residues from about 1 to about 138, inclusive of Figure 90 (SEQ ID NO:153), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA50177 comprising the nucleotide sequence of Figure 91 (SEQ ID NO:154).

### 35. PRO1016

A cDNA clone (DNA56113-1378) has been identified, having sequence identity with acyltransferases that encodes a novel polypeptide, designated in the present application as "PRO1016".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1016 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1016 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 378, inclusive of Figure 93 (SEQ ID NO:156), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-378, or in another embodiment, 19-378.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1016 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 168 or 222 and about 1301, inclusive, of Figure 92 (SEQ ID NO:155). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule



encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203049 (DNA56113-1378), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203049 (DNA56113-1378).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 19 to about 378, inclusive of Figure 93 (SEQ ID NO:156), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1016 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 378, inclusive of Figure 93 (SEQ ID NO:156), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA  
15 molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1016 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domains deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position  
20 1 through about amino acid position 18 in the sequence of Figure 93 (SEQ ID NO:156). The transmembrane domains have been tentatively identified as extending from about amino acid position 305 through about amino acid position 330 and from about amino acid position 332 through about amino acid position 352 in the PRO1016 amino acid sequence (Figure 93, SEQ ID NO:156).

25 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 19 to about 378, inclusive of Figure 93 (SEQ ID NO:156), or (b) the complement of the DNA of (a).

30 In another embodiment, the invention provides isolated PRO1016 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1016 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 19 through 378 of Figure 93 (SEQ ID NO:156).

35 In another aspect, the invention concerns an isolated PRO1016 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 19 to about 378, inclusive of Figure 93 (SEQ ID NO:156).



In a further aspect, the invention concerns an isolated PRO1016 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 19 through 378 of Figure 93 (SEQ ID NO:156).

5 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1016 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 378, inclusive of Figure 93 (SEQ ID NO:156), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell  
10 comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1016 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1016 antibody.

15 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1016 polypeptide, by contacting the native PRO1016 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1016 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

## 20 36. PRO1013

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with P120, wherein the polypeptide is designated in the present application as "PRO1013".

25 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1013 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1013 polypeptide having amino acid residues 1 through 409 of Figure 95 (SEQ ID NO:158), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on June 2, 1998 with the ATCC as DNA56410-1414 which includes the nucleotide sequence encoding PRO1013.

30 In another embodiment, the invention provides isolated PRO1013 polypeptide. In particular, the invention provides isolated native sequence PRO1013 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 409 of Figure 95 (SEQ ID NO:158). Optionally, the PRO1013 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on June 2, 1998 with the ATCC as DNA56410-1414.

35

**37. PRO937**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to glypican family proteins, wherein the polypeptide is designated in the present application as "PRO937".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO937 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO937 polypeptide having amino acid residues 1 to 556 of Figure 97 (SEQ ID NO:160), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO937 polypeptide having amino acid residues about 23 to 556 of Figure 97 (SEQ ID NO:160), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA56436-1448 vector deposited on May 27, 1998, as ATCC 209902 which includes the nucleotide sequence encoding PRO937.

In another embodiment, the invention provides isolated PRO937 polypeptide. In particular, the invention provides isolated native sequence PRO937 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 556 of Figure 97 (SEQ ID NO:160). Additional embodiments of the present invention are directed to PRO937 polypeptides comprising amino acids about 23 to 556 of Figure 97 (SEQ ID NO:160). Optionally, the PRO937 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA56436-1448 vector deposited on May 27, 1998 as ATCC 209902.

**38. PRO842**

A cDNA clone (DNA56855-1447) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO842."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO842 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO842 polypeptide having the sequence of amino acid residues from about 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO842 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 219 and about 509, inclusive, of Figure 98 (SEQ ID NO:164). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule

encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203004 (DNA56855-1447), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203004 (DNA56855-1447).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides, and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO842 polypeptide having the sequence of amino acid residues from about 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most  
15 preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO842 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1  
20 through about amino acid position 22 in the sequence of Figure 99 (SEQ ID NO:165).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165), or (b) the  
25 complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO842 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

30 In another embodiment, the invention provides isolated PRO842 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO842 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 23 to 119 of Figure 99 (SEQ ID NO:165).

In another aspect, the invention concerns an isolated PRO842 polypeptide, comprising an amino acid  
35 sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165).

In a further aspect, the invention concerns an isolated PRO842 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 to 119 of Figure 99 (SEQ ID NO:165).

5 In yet another aspect, the invention concerns an isolated PRO842 polypeptide, comprising the sequence of amino acid residues 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165), or a fragment thereof sufficient to provide a binding site for an anti-PRO842 antibody. Preferably, the PRO842 fragment retains a qualitative biological activity of a native PRO842 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO842 polypeptide having the sequence of amino acid residues from about 23 to about 119, inclusive of Figure 99 (SEQ ID NO:165), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the  
15 polypeptide from the cell culture.

### 39. PRO839

A cDNA clone (DNA56859-1445) has been identified that encodes a novel polypeptide, designated in the present application as "PRO839."

20 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO839 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO839 polypeptide having  
25 the sequence of amino acid residues from about 24 to about 87, inclusive of Figure 101 (SEQ ID NO:167), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO839 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 71 and about 262, inclusive, of Figure 100 (SEQ ID NO:166). Preferably, hybridization occurs under stringent  
30 hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203019  
35 (DNA56859-1445), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203019 (DNA56859-1445).



In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 24 to about 87, inclusive of Figure 101 (SEQ ID NO:167), or the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 50 nucleotides, and preferably at least 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO839 polypeptide having the sequence of amino acid residues from about 24 to about 87, inclusive of Figure 101 (SEQ ID NO: 167), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least  
10 about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO839 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic  
15 acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 23 in the sequence of Figure 101 (SEQ ID NO:167).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
20 amino acid sequence of residues 24 to about 87, inclusive of Figure 101 (SEQ ID NO:167), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO839 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
25 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO839 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO839 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 24 to 87 of Figure 101 (SEQ ID NO:167).

30 In another aspect, the invention concerns an isolated PRO839 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 24 to about 87, inclusive of Figure 101 (SEQ ID NO:167).

In a further aspect, the invention concerns an isolated PRO839 polypeptide, comprising an amino acid  
35 sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 24 to 87 of Figure 101 (SEQ ID NO:167).

In yet another aspect, the invention concerns an isolated PRO839 polypeptide, comprising the sequence of amino acid residues 24 to about 87, inclusive of Figure 101 (SEQ ID NO:167), or a fragment thereof sufficient to provide a binding site for an anti-PRO839 antibody. Preferably, the PRO839 fragment retains a qualitative biological activity of a native PRO839 polypeptide.

5 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO839 polypeptide having the sequence of amino acid residues from about 24 to about 87, inclusive of Figure 101 (SEQ ID NO:167), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising  
10 the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

#### 40. PRO1180

Applicants have identified a cDNA clone (DNA56860-1510) having homology to nucleic acid encoding  
15 methyltransferase enzymes that encodes a novel polypeptide, designated in the present application as "PRO1180".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1180 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity,  
20 preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1180 polypeptide having the sequence of amino acid residues from about 1 or about 24 to about 277, inclusive of Figure 103 (SEQ ID NO:169), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1180  
25 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 78 or about 147 and about 908, inclusive of Figure 102 (SEQ ID NO:168). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
30 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209952 (DNA56860-1510). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209952 (DNA56860-1510).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA  
35 encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 277, inclusive of Figure 103 (SEQ ID

NO:169).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1180 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 23 in the sequence of Figure 103 (SEQ ID NO:169).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 24 to about 277, inclusive of Figure 103 (SEQ ID NO:169).

Another embodiment is directed to fragments of a PRO1180 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1180 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1180 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 24 to about 277 of Figure 103 (SEQ ID NO:169).

In another aspect, the invention concerns an isolated PRO1180 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 277, inclusive of Figure 103 (SEQ ID NO:169).

In a further aspect, the invention concerns an isolated PRO1180 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 24 to about 277, inclusive of Figure 103 (SEQ ID NO:169).

In yet another aspect, the invention concerns an isolated PRO1180 polypeptide, comprising the sequence of amino acid residues 1 or about 24 to about 277, inclusive of Figure 103 (SEQ ID NO:169), or a fragment thereof sufficient to provide a binding site for an anti-PRO1180 antibody. Preferably, the PRO1180 fragment retains a qualitative biological activity of a native PRO1180 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1180 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1180 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1180 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1180 polypeptide.



In still a further embodiment, the invention concerns a composition comprising a PRO1180 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**41. PRO1134**

5 A cDNA clone (DNA56865-1491) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1134".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1134 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1134 polypeptide having the sequence of amino acid residues from about 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1134 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 153 or about 222 and about 1265, inclusive, of Figure 104 (SEQ ID NO:170). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203022 (DNA56865-1491) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203022 (DNA56865-1491).

25 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171), or (b) the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1134 polypeptide having the sequence of amino acid residues from 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1134 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is



complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 23 in the sequence of Figure 105 (SEQ ID NO:171).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO1134 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 104 (SEQ ID NO:170).

In another embodiment, the invention provides isolated PRO1134 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

15 In a specific aspect, the invention provides isolated native sequence PRO1134 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 24 to about 371 of Figure 105 (SEQ ID NO:171).

20 In another aspect, the invention concerns an isolated PRO1134 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171).

25 In a further aspect, the invention concerns an isolated PRO1134 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171).

In yet another aspect, the invention concerns an isolated PRO1134 polypeptide, comprising the sequence of amino acid residues 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171), or a fragment thereof sufficient to provide a binding site for an anti-PRO1134 antibody. Preferably, the PRO1134 fragment retains a qualitative biological activity of a native PRO1134 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1134 polypeptide having the sequence of amino acid residues from about 1 or about 24 to about 371, inclusive of Figure 105 (SEQ ID NO:171), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA52352 comprising the nucleotide sequence of SEQ ID NO:172 (see Figure 106).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA55725 comprising the nucleotide sequence of SEQ ID NO:173 (see Figure 107).

5    42.    **PRO830**

A cDNA clone (DNA56866-1342) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO830".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO830 polypeptide.

10        In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO830 polypeptide having the sequence of amino acid residues from about 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175), or (b) the complement of the DNA molecule of (a).

15        In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO830 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 154 or about 253 and about 414, inclusive, of Figure 108 (SEQ ID NO:174). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20        In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203023 (DNA56866-1342) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
25    ATCC Deposit No. 203023 (DNA56866-1342).

30        In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175), or (b) the complement of the DNA of (a).

35        In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO830 polypeptide having the sequence of amino acid residues from 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO830 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 33 in the sequence of Figure 109 (SEQ ID NO:175).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO830 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 108 (SEQ ID NO:174).

15 In another embodiment, the invention provides isolated PRO830 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO830 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 34 to about 87 of Figure 109 (SEQ ID NO:175).

20 In another aspect, the invention concerns an isolated PRO830 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175).

25 In a further aspect, the invention concerns an isolated PRO830 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175).

30 In yet another aspect, the invention concerns an isolated PRO830 polypeptide, comprising the sequence of amino acid residues 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175), or a fragment thereof sufficient to provide a binding site for an anti-PRO830 antibody. Preferably, the PRO830 fragment retains a qualitative biological activity of a native PRO830 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO830 polypeptide having the sequence of amino acid residues from about 1 or about 34 to about 87, inclusive of Figure 109 (SEQ ID NO:175), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host



cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

#### 43. PRO1115

5 A cDNA clone (DNA56868-1478) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO1115".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1115 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1115 polypeptide having the sequence of amino acid residues from about 21 to about 445, inclusive of Figure 111 (SEQ ID NO:177), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1115 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 249 and about 1523, inclusive, of Figure 110 (SEQ ID NO:176). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203024 (DNA56868-1478), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203024 (DNA56868-1478).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 21 to about 445, inclusive of Figure 111 (SEQ ID NO:177), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1115 polypeptide having the sequence of amino acid residues from about 21 to about 445, inclusive of Figure 111 (SEQ ID NO: 177), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1115 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and



one or more of its transmembrane domains deleted or inactivated, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 20 in the sequence of Figure 111 (SEQ ID NO: 177). Transmembrane domains have been tentatively identified as extending from about amino acid positions 35-54, 75-97, 126-146, 185-204, 333-350, and 352-371 in the PRO1115 amino acid sequence (Figure 111, SEQ ID NO: 177).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 21 to about 445, inclusive of Figure 111 (SEQ ID NO:177), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO1115 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

15 In another embodiment, the invention provides isolated PRO1115 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1115 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 21 to 445 of Figure 111 (SEQ ID NO:177).

20 In another aspect, the invention concerns an isolated PRO1115 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 21 to about 445, inclusive of Figure 111 (SEQ ID NO:177).

25 In a further aspect, the invention concerns an isolated PRO1115 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 21 to 445 of Figure 111 (SEQ ID NO:177).

In yet another aspect, the invention concerns an isolated PRO1115 polypeptide, comprising the sequence of amino acid residues 21 to about 445, inclusive of Figure 111 (SEQ ID NO:177), or a fragment thereof sufficient to provide a binding site for an anti-PRO1115 antibody. Preferably, the PRO1115 fragment retains a qualitative biological activity of a native PRO1115 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1115 polypeptide having the sequence of amino acid residues from about 21 to about 445, inclusive of Figure 111 (SEQ ID NO:177), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence  
35 identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

**44. PRO1277**

A cDNA clone (DNA56869-1545) has been identified that encodes a novel polypeptide having homology to Coch-5B2 and designated in the present application as "PRO1277."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1277 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1277 polypeptide having the sequence of amino acid residues from about 27 to about 678, inclusive of Figure 113 (SEQ ID NO:179), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1277 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 266 and about 2221, inclusive, of Figure 112 (SEQ ID NO:178). Preferably, hybridization occurs under stringent hybridization and wash conditions.

15 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203161 (DNA56869-1545), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
20 Deposit No. 203161 (DNA56869-1545).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 27 to about 678, inclusive of Figure 113 (SEQ ID  
25 NO:179), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1277 polypeptide having the sequence of amino acid residues from about 27 to about 678, inclusive of Figure 113 (SEQ ID NO:179), or (b) the  
30 complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1277 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and  
35 its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 26 in the sequence of Figure 113 (SEQ ID NO:179). The transmembrane

domain has been tentatively identified as extending from about amino acid position 181 to about amino acid position 200 in the PRO1277 amino acid sequence (Figure 113, SEQ ID NO:179).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 27 to about 678, inclusive of Figure 113 (SEQ ID NO:179), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1277 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1277 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1277 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 27 to 678 of Figure 113 (SEQ ID NO:179).

In another aspect, the invention concerns an isolated PRO1277 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 27 to about 678, inclusive of Figure 113 (SEQ ID NO:179).

In a further aspect, the invention concerns an isolated PRO1277 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 27 to 678 of Figure 113 (SEQ ID NO:179).

In yet another aspect, the invention concerns an isolated PRO1277 polypeptide, comprising the sequence of amino acid residues 27 to about 678, inclusive of Figure 113 (SEQ ID NO:179), or a fragment thereof sufficient to provide a binding site for an anti-PRO1277 antibody. Preferably, the PRO1277 fragment retains a qualitative biological activity of a native PRO1277 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1277 polypeptide having the sequence of amino acid residues from about 27 to about 678, inclusive of Figure 113 (SEQ ID NO:179), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1277 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1277 antibody.



In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1277 polypeptide, by contacting the native PRO1277 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1277 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

5  
45. **PRO1135**

Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to alpha 1,2-mannosidase, wherein the polypeptide is designated in the present application as "PRO1135".

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1135 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1135 polypeptide having amino acid residues 1 to 541 of Figure 115 (SEQ ID NO:181), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1135 polypeptide having amino acid residues about 22 to 541 of Figure 115 (SEQ ID NO:181), or is complementary  
15 to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA56870-1492 vector deposited on June 2, 1998 as ATCC 209925 which includes the nucleotide sequence encoding PRO1135.

20 In another embodiment, the invention provides isolated PRO1135 polypeptide. In particular, the invention provides isolated native sequence PRO1135 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 541 of Figure 115 (SEQ ID NO:181). Additional embodiments of the present invention are directed to PRO1135 polypeptides comprising amino acids about 22 to 541 of Figure 115 (SEQ ID NO:181). Optionally, the PRO1135 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA56870-1492 vector deposited on June 2, 1998 as ATCC  
25 209925.

46. **PRO1114**

A cDNA clone (DNA57033-1403) has been identified that encodes a novel interferon receptor polypeptide, designated in the present application as "PRO1114 interferon receptor".

30 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 interferon receptor polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1114 interferon receptor  
35 polypeptide having the sequence of amino acid residues from about 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183), or (b) the complement of the DNA molecule of (a).



In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1114 interferon receptor polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 250 or about 337 and about 1182, inclusive, of Figure 116 (SEQ ID NO:182). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209905 (DNA57033-1403) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
10 ATCC Deposit No. 209905 (DNA57033-1403).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID  
15 NO:183), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183), or (b) the complement of the DNA  
20 molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1114 interferon receptor polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 29 in the sequence of Figure 117 (SEQ ID NO:183). The transmembrane domain has been tentatively identified as extending from about amino acid position 230 to about amino acid position 255 in the PRO1114 interferon receptor amino acid sequence (Figure 117, SEQ ID  
25 NO:183).  
30 NO:183).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183), or (b)  
35 the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1114 interferon receptor polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80

nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 116 (SEQ ID NO:182).

In another embodiment, the invention provides isolated PRO1114 interferon receptor polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

5 In a specific aspect, the invention provides isolated native sequence PRO1114 interferon receptor polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 30 to about 311 of Figure 117 (SEQ ID NO:183).

10 In another aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183).

15 In a further aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183).

20 In yet another aspect, the invention concerns an isolated PRO1114 interferon receptor polypeptide, comprising the sequence of amino acid residues 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183), or a fragment thereof sufficient to provide a binding site for an anti-PRO1114 interferon receptor antibody. Preferably, the PRO1114 interferon receptor fragment retains a qualitative biological activity of a native PRO1114 interferon receptor polypeptide.

25 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1114 interferon receptor polypeptide having the sequence of amino acid residues from about 1 or about 30 to about 311, inclusive of Figure 117 (SEQ ID NO:183), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

30 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1114 interferon receptor polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1114 interferon receptor antibody.

35 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1114 interferon receptor polypeptide by contacting the native PRO1114 interferon receptor polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1114 interferon receptor polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically

acceptable carrier.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA48466 comprising the nucleotide sequence of SEQ ID NO:184 (see Figure 118).

47. **PRO828**

5 Applicants have identified a cDNA clone that encodes a novel polypeptide having homology to glutathione peroxidases wherein the polypeptide is designated in the present application as "PRO828".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO828 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO828 polypeptide having amino acid residues 1 to 187 of Figure 120 (SEQ ID NO:189), or is complementary to such  
10 encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO828 polypeptide having amino acid residues about 22 to 187 of Figure 120 (SEQ ID NO:189), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the  
15 DNA57037-1444 vector deposited on May 27, 1998 as ATCC 209903 which includes the nucleotide sequence encoding PRO828.

In another embodiment, the invention provides isolated PRO828 polypeptide. In particular, the invention provides isolated native sequence PRO828 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 187 of Figure 120 (SEQ ID NO:189). Additional embodiments of the  
20 present invention are directed to PRO828 polypeptides comprising amino acids about 22 to 187 of Figure 120 (SEQ ID NO:189). Optionally, the PRO828 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA57037-1444 vector deposited on May 27, 1998 as ATCC 209903.

25 48. **PRO1009**

A cDNA clone (DNA57129-1413) has been identified, having sequence identity with a long chain acyl-CoA synthetase homologue, a long chain acyl-CoA synthetase and a long chain acyl-CoA synthetase ligase that encodes a novel polypeptide, designated in the present application as "PRO1009."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding  
30 a PRO1009 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1009 polypeptide having the sequence of amino acid residues from about 1 or 23 to about 615, inclusive of Figure 122 (SEQ ID NO:194),  
35 or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two separate alternative embodiments provided herein, i.e., 1-615 or 23-615.



In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1009 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 41 or 107 and about 1885, inclusive, of Figure 121 (SEQ ID NO:193). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209977 (DNA57129-1413), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
10 Deposit No. 209977 (DNA57129-1413).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 23 to about 615, inclusive of Figure 122 (SEQ  
15 ID NO:194), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1009 polypeptide having the sequence of amino acid residues from about 1 or 23 to about 615, inclusive of Figure 122 (SEQ ID NO:194), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an  
20 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1009 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and  
25 its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 to about amino acid position 22 in the sequence of Figure 122 (SEQ ID NO:194). The transmembrane domains have been tentatively identified as extending from about amino acid positions 140-161, 213-229 and 312-334 in the PRO1009 amino acid sequence (Figure 122, SEQ ID NO:194).

30 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 23 to about 615, inclusive of Figure 122 (SEQ ID NO:194), or (b) the complement of the DNA of (a).

35 In another embodiment, the invention provides isolated PRO1009 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.



In a specific aspect, the invention provides isolated native sequence PRO1009 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 23 to 615 of Figure 122 (SEQ ID NO:194).

5 In another aspect, the invention concerns an isolated PRO1009 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 23 to about 615, inclusive of Figure 122 (SEQ ID NO:194).

10 In a further aspect, the invention concerns an isolated PRO1009 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 23 to 615 of Figure 122 (SEQ ID NO:194).

In yet another aspect, the invention concerns an isolated PRO1009 polypeptide, comprising the sequence of amino acid residues 1 or 23 to about 615, inclusive of Figure 122 (SEQ ID NO:194), or a fragment thereof sufficient to provide a binding site for an anti-PRO1009 antibody. Preferably, the PRO1009 fragment retains a qualitative biological activity of a native PRO1009 polypeptide.

15 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1009 polypeptide having the sequence of amino acid residues from about 1 or 23 through about 615, inclusive of Figure 122 (SEQ ID NO:194), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 20 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1009 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1009 antibody.

25 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1009 polypeptide, by contacting the native PRO1009 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1009 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

30 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA50853 comprising the nucleotide sequence of Figure 123 (SEQ ID NO:195).

#### 49. PRO1007

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with 35 MAGPIAP, wherein the polypeptide is designated in the present application as "PRO1007".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1007 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1007

polypeptide having amino acid residues 1 through 346 of Figure 125 (SEQ ID NO:197), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on June 9, 1998 with the ATCC as DNA57690-1374 which includes the nucleotide sequence encoding PRO1007.

5 In another embodiment, the invention provides isolated PRO1007 polypeptide. In particular, the invention provides isolated native sequence PRO1007 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 346 of Figure 125 (SEQ ID NO:197). An additional embodiment of the present invention is directed to an isolated extracellular domain of a PRO1007 polypeptide. Optionally, the PRO1007 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert  
10 of the vector deposited with the ATCC on June 9, 1998 as DNA57690-1374.

#### 50. PRO1056

A cDNA clone (DNA57693-1424) has been identified, having homology to nucleic acid encoding a chloride channel protein that encodes a novel polypeptide, designated in the present application as "PRO1056".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1056 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1056 polypeptide having  
20 the sequence of amino acid residues from about 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1056 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 56 or about 110 and about 415, inclusive, of Figure 126 (SEQ ID NO:198). Preferably, hybridization occurs under  
25 stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203008  
30 (DNA57693-1424) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203008 (DNA57693-1424).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
35 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1056 polypeptide having the sequence of amino acid residues from 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1056 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 18 in the sequence of Figure 127 (SEQ ID NO:199). The transmembrane domain has been tentatively identified as extending from about amino acid position 39 to about amino acid position 58 in the PRO1056 amino acid sequence (Figure 127, SEQ ID NO:199).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1056 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 126 (SEQ ID NO:198).

In another embodiment, the invention provides isolated PRO1056 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1056 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 19 to about 120 of Figure 127 (SEQ ID NO:199).

In another aspect, the invention concerns an isolated PRO1056 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199).

In a further aspect, the invention concerns an isolated PRO1056 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199).



In yet another aspect, the invention concerns an isolated PRO1056 polypeptide, comprising the sequence of amino acid residues 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199), or a fragment thereof sufficient to provide a binding site for an anti-PRO1056 antibody. Preferably, the PRO1056 fragment retains a qualitative biological activity of a native PRO1056 polypeptide.

5 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1056 polypeptide having the sequence of amino acid residues from about 1 or about 19 to about 120, inclusive of Figure 127 (SEQ ID NO:199), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host  
10 cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1056 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1056 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a  
15 native PRO1056 polypeptide by contacting the native PRO1056 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1056 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

20 **51. PRO826**

A cDNA clone (DNA57694-1341) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO826".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding  
25 a PRO826 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO826 polypeptide having the sequence of amino acid residues from about 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201), or (b) the complement of the DNA molecule of (a).

30 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO826 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 13 or about 79 and about 309, inclusive, of Figure 128 (SEQ ID NO:200). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
35 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203017



(DNA57694-1341) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203017 (DNA57694-1341).

5 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201), or (b) the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO826 polypeptide having the sequence of amino acid residues from 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO826 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 22 in the sequence of Figure 129 (SEQ ID NO:201).

20 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201), or (b) the complement of the DNA of (a).

25 Another embodiment is directed to fragments of a PRO826 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 128 (SEQ ID NO:200).

30 In another embodiment, the invention provides isolated PRO826 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO826 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 23 to about 99 of Figure 129 (SEQ ID NO:201).

35 In another aspect, the invention concerns an isolated PRO826 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the

sequence of amino acid residues 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201).

In a further aspect, the invention concerns an isolated PRO826 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201).

5 In yet another aspect, the invention concerns an isolated PRO826 polypeptide, comprising the sequence of amino acid residues 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201), or a fragment thereof sufficient to provide a binding site for an anti-PRO826 antibody. Preferably, the PRO826 fragment retains a qualitative biological activity of a native PRO826 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO826 polypeptide having the sequence of amino acid residues from about 1 or about 23 to about 99, inclusive of Figure 129 (SEQ ID NO:201), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host  
15 cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

## 52. PRO819

20 A cDNA clone (DNA57695-1340) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO819".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO819 polypeptide.

25 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO819 polypeptide having the sequence of amino acid residues from about 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203), or (b) the complement of the DNA molecule of (a).

30 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO819 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 46 or about 118 and about 201, inclusive, of Figure 130 (SEQ ID NO:202). Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203006 (DNA57695-1340) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in

ATCC Deposit No. 203006 (DNA57695-1340).

5 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203), or (b) the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO819 polypeptide having the sequence of amino acid residues from 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO819 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 24 in the sequence of Figure 131 (SEQ ID NO:203).

20 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203), or (b) the complement of the DNA of (a).

25 Another embodiment is directed to fragments of a PRO819 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 130 (SEQ ID NO:202).

In another embodiment, the invention provides isolated PRO819 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

30 In a specific aspect, the invention provides isolated native sequence PRO819 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 25 to about 52 of Figure 131 (SEQ ID NO:203).

35 In another aspect, the invention concerns an isolated PRO819 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203).



In a further aspect, the invention concerns an isolated PRO819 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203).

5 In yet another aspect, the invention concerns an isolated PRO819 polypeptide, comprising the sequence of amino acid residues 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203), or a fragment thereof sufficient to provide a binding site for an anti-PRO819 antibody. Preferably, the PRO819 fragment retains a qualitative biological activity of a native PRO819 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO819 polypeptide having the sequence of amino acid residues from about 1 or about 25 to about 52, inclusive of Figure 131 (SEQ ID NO:203), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) 15 recovering the polypeptide from the cell culture.

### 53. PRO1006

A cDNA clone (DNA57699-1412) has been identified, having sequence identity with a virud protein believed to be a tyrosine protein kinase, that encodes a novel polypeptide, designated in the present application 20 as "PRO1006."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1006 polypeptide.

25 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1006 polypeptide having the sequence of amino acid residues from about 1 or 24 to about 392, inclusive of Figure 133 (SEQ ID NO:205), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-392, or in another embodiment, 24-392.

30 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1006 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 28 or 97 and about 1203, inclusive, of Figure 132 (SEQ ID NO:204). Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203020



(DNA57699-1412), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203020 (DNA57699-1412).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 24 to about 392, inclusive of Figure 133 (SEQ ID NO:205), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1006 polypeptide having the sequence of amino acid residues from about 1 or 24 to about 392, inclusive of Figure 133 (SEQ ID NO:205), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 24 to about 392, inclusive of Figure 133 (SEQ ID NO:205), or (b) the complement of the DNA of (a).

20 In another embodiment, the invention provides isolated PRO1006 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1006 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 24 through 392 of Figure 133 (SEQ ID NO:205).

25 In another aspect, the invention concerns an isolated PRO1006 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 24 to about 392, inclusive of Figure 133 (SEQ ID NO:205).

30 In a further aspect, the invention concerns an isolated PRO1006 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 24 through 392 of Figure 133 (SEQ ID NO:205).

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1006 polypeptide having the sequence of amino acid residues from about 1 or 24 to about 392, inclusive of Figure 133 (SEQ ID NO:205), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90%

sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1006 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1006 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1006 polypeptide, by contacting the native PRO1006 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1006 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

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#### 54. PRO1112

Applicants have identified a cDNA clone that encodes a novel polypeptide having multiple transmembranedomains and having some sequence identity with a Mycobacterium tuberculosis peptide, a peptide found in a Dayhoff database designated as "MTY20B11\_13", wherein the novel polypeptide is designated in the present application as "PRO1112".

15

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1112 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1112 polypeptide having the sequence of amino acid residues from 1 or about 14 through about 262 of Figure 135 (SEQ ID NO:207), or (b) the complement of the DNA molecule of (a).

20

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1112 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues about 20 or 59 through 809 of Figure 134 (SEQ ID NO:206). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in the ATCC Deposit of DNA57702-1476 made on June 9, 1998. In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in the ATCC Deposit of DNA57702-1476 made on June 9, 1998.

30

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 14 through about 262 of Figure 135 (SEQ ID

35

NO:207).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1112 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domains deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 13 of Figure 135 (SEQ ID NO:207). The transmembrane domains have been tentatively identified as extending from about amino acid positions 58-76, 99-113, 141-159 and 203-222 of Figure 135 (SEQ ID NO:207).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 14 through 262 of Figure 135 (SEQ ID NO:207).

Another embodiment is directed to fragments of a PRO1112 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 60 to about 100 nucleotides in length.

In another embodiment, the invention provides isolated PRO1112 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1112 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 14 through about 262 of Figure 135 (SEQ ID NO:207).

In another aspect, the invention concerns an isolated PRO1112 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 14 through about 262 of Figure 135 (SEQ ID NO:207).

In a further aspect, the invention concerns an isolated PRO1112 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 14 through about 262 of Figure 135 (SEQ ID NO:207).

In yet another aspect, the invention concerns an isolated PRO1112 polypeptide, comprising the sequence of amino acid residues 1 or about 14 through about 262 of Figure 135 (SEQ ID NO:207), or a fragment thereof sufficient to provide a binding site for an anti-PRO1112 antibody. Preferably, the PRO1112 fragment retains a qualitative biological activity of a native PRO1112 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1112 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

#### 55. PRO1074

Applicants have identified a cDNA clone, DNA57704-1452, that encodes a novel polypeptide having homology to galactosyltransferase, wherein the polypeptide is designated in the present application as "PRO1074".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1074 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1074 polypeptide having the sequence of amino acid residues from 1 to about 331, inclusive of Figure 137 (SEQ ID NO:209), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1074 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence having about residues 322 to 1314, inclusive of Figure 136 (SEQ ID NO:208). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209953 (DNA57704-1452), which was deposited on June 9, 1998, or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209953 (DNA57704-1452).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 331, inclusive of Figure 137 (SEQ ID NO:209).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1074 extracellular domain (ECD), with or without the initiating methionine, and its soluble variants (i.e. transmembrane domain(s) deleted or inactivated) or is complementary to such encoding nucleic acid molecule. A type II transmembrane domain region has been tentatively identified as extending from about amino acid position 20 to 39 in the PRO1074 amino acid sequence (Figure 137, SEQ ID NO:209).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, and most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 331, inclusive of Figure 137 (SEQ ID NO:209).

Another embodiment is directed to fragments of a PRO1074 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1074 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.



In a specific aspect, the invention provides isolated native sequence PRO1074 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 331 of Figure 137 (SEQ ID NO:209).

In another aspect, the invention concerns an isolated PRO1074 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to 331, inclusive of Figure 137 (SEQ ID NO:209).

In a further aspect, the invention concerns an isolated PRO1074 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, and most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 331 of Figure 137 (SEQ ID NO:209).

In another aspect, the invention concerns a PRO1074 extracellular domain comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues X to 331 of Figure 2 (SEQ ID NO:3), wherein X is any one of amino acid residues 35 to 44 of Figure 137 (SEQ ID NO:209).

In yet another aspect, the invention concerns an isolated PRO1074 polypeptide, comprising the sequence of amino acid residues 1 to about 331, inclusive of Figure 137 (SEQ ID NO:209), or a fragment thereof sufficient to provide a binding site for an anti-PRO1074 antibody. Preferably, the PRO1074 fragment retains a qualitative biological activity of a native PRO1074 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1074 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

In yet another embodiment, the invention concerns agonist and antagonists of the PRO1074 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1074 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1074 polypeptide.

In still a further embodiment, the invention concerns a composition comprising a PRO1074 polypeptide as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 56. PRO1005

A cDNA clone (DNA57708-1411) has been identified that encodes a novel polypeptide, designated in the present application as "PRO1005."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1005 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1005 polypeptide having the sequence of amino acid residues from about 21 to about 185, inclusive of Figure 139 (SEQ ID NO:211), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1005 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 90 and about 584, inclusive, of Figure 138 (SEQ ID NO:210). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203021 (DNA57708-1411), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
10 Deposit No. 203021 (DNA57708-1411).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 21 to about 185, inclusive of Figure 139 (SEQ ID  
15 NO:211), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 50 nucleotides, and preferably at least 100 nucleotides, and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1005 polypeptide having the sequence of amino acid residues from about 21 to about 185, inclusive of Figure 139 (SEQ ID NO:211), or (b) the complement of  
20 the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1005 polypeptide, with or without the N-terminal signal sequence, or is complementary to such encoding  
25 nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 20 in the sequence of Figure 139 (SEQ ID NO:211).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
30 amino acid sequence of residues 21 to about 185, inclusive of Figure 139 (SEQ ID NO:211), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1005 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
35 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1005 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1005 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 21 to 185 of Figure 139 (SEQ ID NO:211).

In another aspect, the invention concerns an isolated PRO1005 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 21 to about 185, inclusive of Figure 139 (SEQ ID NO:211).

In a further aspect, the invention concerns an isolated PRO1005 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 21 to 185 of Figure 139 (SEQ ID NO:211).

In yet another aspect, the invention concerns an isolated PRO1005 polypeptide, comprising the sequence of amino acid residues 21 to about 185, inclusive of Figure 139 (SEQ ID NO:211), or a fragment thereof sufficient to provide a binding site for an anti-PRO1005 antibody. Preferably, the PRO1005 fragment retains a qualitative biological activity of a native PRO1005 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1005 polypeptide having the sequence of amino acid residues from about 21 to about 185, inclusive of Figure 139 (SEQ ID NO:211), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

#### 57. PRO1073

A cDNA clone (DNA57710-1451) has been identified that encodes a novel polypeptide, designated in the present application as "PRO1073."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1073 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1073 polypeptide having the sequence of amino acid residues from about 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1073 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 438 and about 1241, inclusive, of Figure 140 (SEQ ID NO:212). Preferably, hybridization occurs under stringent hybridization and wash conditions.



In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203048 (DNA57710-1451), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203048 (DNA57710-1451).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1073 polypeptide having the sequence of amino acid residues from about 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1073 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 31 in the sequence of Figure 141 (SEQ ID NO:213).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1073 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1073 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1073 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 32 to 299 of Figure 141 (SEQ ID NO:213).



In another aspect, the invention concerns an isolated PRO1073 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213).

5 In a further aspect, the invention concerns an isolated PRO1073 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 32 to 299 of Figure 141 (SEQ ID NO:213).

10 In yet another aspect, the invention concerns an isolated PRO1073 polypeptide, comprising the sequence of amino acid residues 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213), or a fragment thereof sufficient to provide a binding site for an anti-PRO1073 antibody. Preferably, the PRO1073 fragment retains a qualitative biological activity of a native PRO1073 polypeptide.

15 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1073 polypeptide having the sequence of amino acid residues from about 32 to about 299, inclusive of Figure 141 (SEQ ID NO:213), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

20

#### 58. PRO1152

A cDNA clone (DNA57711-1501) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO1152".

25 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1152 polypeptide.

30 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1152 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1152 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 58 or about 142 and about 1494, inclusive, of Figure 143 (SEQ ID NO:215). Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule

encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203047 (DNA57711-1501) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203047 (DNA57711-1501).

5 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216), or (b) the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 300 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1152 polypeptide having the sequence of amino acid residues from 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence  
15 identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1152 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid  
20 position 1 to about amino acid position 28 in the sequence of Figure 144 (SEQ ID NO:216). The various transmembrane domains have been tentatively identified as extending from about amino acid position 133 to about amino acid position 155, from about amino acid position 168 to about amino acid position 187, from about amino acid position 229 to about amino acid position 247, from about amino acid position 264 to about amino acid position 285, from about amino acid position 309 to about amino acid position 330, from about amino acid  
25 position 371 to about amino acid position 390 and from about amino acid position 441 to about amino acid position 464 in the PRO1152 amino acid sequence (Figure 144, SEQ ID NO:216).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
30 amino acid sequence of residues 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1152 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
35 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 143 (SEQ ID NO:215).

In another embodiment, the invention provides isolated PRO1152 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1152 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 29 to about 479 of Figure 144 (SEQ ID NO:216).

5 In another aspect, the invention concerns an isolated PRO1152 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216).

10 In a further aspect, the invention concerns an isolated PRO1152 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216).

15 In yet another aspect, the invention concerns an isolated PRO1152 polypeptide, comprising the sequence of amino acid residues 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216), or a fragment thereof sufficient to provide a binding site for an anti-PRO1152 antibody. Preferably, the PRO1152 fragment retains a qualitative biological activity of a native PRO1152 polypeptide.

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1152 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 479, inclusive of Figure 144 (SEQ ID NO:216), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

25 In another embodiment, the invention provides a nucleic acid molecule designated herein as DNA55807 comprising the nucleotide sequence of SEQ ID NO:217 (see Figure 145).

## 59. PRO1136

30 A cDNA clone (DNA57827-1493) has been identified, having homology to nucleic acid encoding PDZ domain-containing proteins that encodes a novel polypeptide, designated in the present application as "PRO1136".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1136 polypeptide.

35 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1136 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID



NO:219), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1136 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 216 or about 261 and about 2111, inclusive, of Figure 146 (SEQ ID NO:218). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203045 (DNA57827-1493) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the  
10 nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203045 (DNA57827-1493).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
15 identity to the sequence of amino acid residues 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID NO:219), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1136 polypeptide having the sequence of amino acid residues from 1 or about 16 to  
20 about 632, inclusive of Figure 147 (SEQ ID NO:219), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding  
25 a PRO1136 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 15 in the sequence of Figure 147 (SEQ ID NO:219).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA  
30 encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID NO:219), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1136 polypeptide coding sequence that may find  
35 use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived



from the nucleotide sequence shown in Figure 146 (SEQ ID NO:218).

In another embodiment, the invention provides isolated PRO1136 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

5 In a specific aspect, the invention provides isolated native sequence PRO1136 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 16 to about 632 of Figure 147 (SEQ ID NO:219).

In another aspect, the invention concerns an isolated PRO1136 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID NO:219).

10 In a further aspect, the invention concerns an isolated PRO1136 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID NO:219).

15 In yet another aspect, the invention concerns an isolated PRO1136 polypeptide, comprising the sequence of amino acid residues 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID NO:219), or a fragment thereof sufficient to provide a binding site for an anti-PRO1136 antibody. Preferably, the PRO1136 fragment retains a qualitative biological activity of a native PRO1136 polypeptide.

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1136 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 632, inclusive of Figure 147 (SEQ ID NO:219), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii)  
25 recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1136 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1136 antibody.

30 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1136 polypeptide by contacting the native PRO1136 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1136 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 60. PRO813

35 Applicants have identified a cDNA clone (DNA57834-1339) having homology to pulmonary surfactant-associated protein C that encodes a novel polypeptide, designated in the present application as "PRO813".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO813 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO813 polypeptide having the sequence of amino acid residues from about 1 or about 27 to about 176, inclusive of Figure 149 (SEQ ID NO:221), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO813 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 109 or about 187 and about 636, inclusive, of Figure 148 (SEQ ID NO:220). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209954 (DNA57834-1339). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209954 (DNA57834-1339).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 27 to about 176, inclusive of Figure 149 (SEQ ID NO:221).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO813 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 26 in the sequence of Figure 149 (SEQ ID NO:221).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 27 to about 176, inclusive of Figure 149 (SEQ ID NO:221).

Another embodiment is directed to fragments of a PRO813 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO813 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO813 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 27 to about 176 of Figure 149 (SEQ ID NO:221).

5 In another aspect, the invention concerns an isolated PRO813 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 27 to about 176, inclusive of Figure 149 (SEQ ID NO:221).

10 In a further aspect, the invention concerns an isolated PRO813 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 27 to about 176, inclusive of Figure 149 (SEQ ID NO:221).

In yet another aspect, the invention concerns an isolated PRO813 polypeptide, comprising the sequence of amino acid residues 1 or about 27 to about 176, inclusive of Figure 149 (SEQ ID NO:221), or a fragment thereof sufficient to provide a binding site for an anti-PRO813 antibody. Preferably, the PRO813 fragment retains a qualitative biological activity of a native PRO813 polypeptide.

15 In another aspect, the present invention is directed to fragments of a PRO813 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO813 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO813 antibody.

20 In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO813 polypeptide.

In still a further embodiment, the invention concerns a composition comprising a PRO813 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 61. PRO809

25 A cDNA clone (DNA57836-1338) has been identified, having sequence identity with heparan sulfate proteoglycans, that encodes a novel polypeptide, designated in the present application as "PRO809."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO809 polypeptide.

30 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO809 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 265, inclusive of Figure 151 (SEQ ID NO:223), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-265, or in another embodiment, 35 19-265.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO809 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 63 or

117 and about 867, inclusive, of Figure 150 (SEQ ID NO:222). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule  
5 encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203025 (DNA57836-1338), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203025 (DNA57836-1338).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA  
10 encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 19 to about 265, inclusive of Figure 151 (SEQ ID NO:223), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing  
15 a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO809 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 265, inclusive of Figure 151 (SEQ ID NO:223), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA  
20 molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 19 to about 265, inclusive of Figure 151 (SEQ ID NO:223), or (b) the  
25 complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO809 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO809 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 19 through 265 of Figure 151 (SEQ ID  
30 NO:223).

In another aspect, the invention concerns an isolated PRO809 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 19 to about 265, inclusive of Figure 151 (SEQ ID NO:223).

35 In a further aspect, the invention concerns an isolated PRO809 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence



of residues 1 or 19 through 265 of Figure 151 (SEQ ID NO:223).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO809 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 265, inclusive of Figure 151 (SEQ ID NO:223), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO809 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO809 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO809 polypeptide, by contacting the native PRO809 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO809 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

## 62. PRO791

A cDNA clone (DNA57838-1337) has been identified, having sequence identity with MHC class I antigens that encodes a novel polypeptide, designated in the present application as "PRO791."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO791 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO791 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 246, inclusive of Figure 153 (SEQ ID NO:225), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-246, or in another embodiment, 26-246.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO791 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 9 or 84 and about 746, inclusive, of Figure 152 (SEQ ID NO:224). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203014 (DNA57838-1337), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic

acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203014 (DNA57838-1337).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 26 to about 246, inclusive of Figure 153 (SEQ ID NO:225), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO791 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 246, inclusive of Figure 153 (SEQ ID NO:225), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 26 to about 246, inclusive of Figure 153 (SEQ ID NO:225), or (b) the complement of the DNA of (a).

20 In another embodiment, the invention provides isolated PRO791 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO791 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 26 through 246 of Figure 153 (SEQ ID NO:225).

25 In another aspect, the invention concerns an isolated PRO791 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 26 to about 246, inclusive of Figure 153 (SEQ ID NO:225).

30 In a further aspect, the invention concerns an isolated PRO791 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 26 through 246 of Figure 153 (SEQ ID NO:225).

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO791 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 246, inclusive of Figure 153 (SEQ ID NO:225), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell

comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO791 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO791 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO791 polypeptide, by contacting the native PRO791 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO791 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

10 63. PRO1004

A cDNA clone (DNA57844-1410) has been identified that encodes a novel polypeptide, designated in the present application as "PRO1004."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1004 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1004 polypeptide having the sequence of amino acid residues from about 25 to about 115, inclusive of Figure 155 (SEQ ID NO:227), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1004 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 191 and about 463, inclusive, of Figure 154 (SEQ ID NO:226). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203010 (DNA57844-1410), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
30 Deposit No. 203010 (DNA57844-1410).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 25 to about 115, inclusive of Figure 155 (SEQ ID  
35 NO:227), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 50 nucleotides, and preferably at least 100 nucleotides, and produced by hybridizing a test DNA molecule under



stringent conditions with (a) a DNA molecule encoding a PRO1004 polypeptide having the sequence of amino acid residues from about 25 to about 115, inclusive of Figure 155 (SEQ ID NO:227), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1004 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 through about amino acid position 24 in the sequence of Figure 155 (SEQ ID NO:227).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 25 to about 115, inclusive of Figure 155 (SEQ ID NO:227), or (b) the complement of the DNA of (a).

15 Another embodiment of the invention is directed to fragments of a PRO1004 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

20 In another embodiment, the invention provides isolated PRO1004 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1004 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 25 to 115 of Figure 155 (SEQ ID NO:227).

25 In another aspect, the invention concerns an isolated PRO1004 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 25 to about 115, inclusive of Figure 155 (SEQ ID NO:227).

30 In a further aspect, the invention concerns an isolated PRO1004 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 25 to 115 of Figure 155 (SEQ ID NO:227).

In yet another aspect, the invention concerns an isolated PRO1004 polypeptide, comprising the sequence of amino acid residues 25 to about 115, inclusive of Figure 155 (SEQ ID NO:227), or a fragment thereof sufficient to provide a binding site for an anti-PRO1004 antibody. Preferably, the PRO1004 fragment retains a qualitative biological activity of a native PRO1004 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1004 polypeptide having the sequence of amino acid residues from about 25 to about 115, inclusive of Figure 155 (SEQ ID NO:227), or (b)



the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

5

**64. PRO1111**

A cDNA clone (DNA58721-1475) has been identified that encodes a novel polypeptide having sequence identity with LIG and designated in the present application as "PRO1111."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1111 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1111 polypeptide having the sequence of amino acid residues from about 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1111 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 57 and about 2015, inclusive, of Figure 156 (SEQ ID NO:228). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203110 (DNA58721-1475), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic  
25 acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203110 (DNA58721-1475).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1111 polypeptide having the sequence of  
35 amino acid residues from about 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most

preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1111 polypeptide in its soluble form, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domains has been tentatively identified as extending from about amino acid positions 21-40 (type II) and 528-548 in the PRO1111 amino acid sequence (Figure 157, SEQ ID NO:229).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1111 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

15 In another embodiment, the invention provides isolated PRO1111 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1111 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 653 of Figure 157 (SEQ ID NO:229).

20 In another aspect, the invention concerns an isolated PRO1111 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229).

25 In a further aspect, the invention concerns an isolated PRO1111 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 653 of Figure 157 (SEQ ID NO:229).

30 In yet another aspect, the invention concerns an isolated PRO1111 polypeptide, comprising the sequence of amino acid residues 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229), or a fragment thereof sufficient to provide a binding site for an anti-PRO1111 antibody. Preferably, the PRO1111 fragment retains a qualitative biological activity of a native PRO1111 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1111 polypeptide having the sequence of amino acid residues from about 1 to about 653, inclusive of Figure 157 (SEQ ID NO:229), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising

the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1111 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1111 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1111 polypeptide, by contacting the native PRO1111 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1111 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

10 65. PRO1344

A cDNA clone (DNA58723-1588) has been identified, having homology to nucleic acid encoding factor C that encodes a novel polypeptide, designated in the present application as "PRO1344".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1344 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1344 polypeptide having the sequence of amino acid residues from about 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1344 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 26 or about 95 and about 2185, inclusive, of Figure 158 (SEQ ID NO:230). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203133 (DNA58723-1588) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
30 ATCC Deposit No. 203133 (DNA58723-1588).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID  
35 NO:231), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA



molecule encoding a PRO1344 polypeptide having the sequence of amino acid residues from 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1344 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 23 in the sequence of Figure 159 (SEQ ID NO:231).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80 % positives, preferably at least about 85 % positives, more preferably at least about 90 % positives, most preferably at least about 95 % positives when compared with the amino acid sequence of residues 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231), or (b) the complement of the DNA of (a).

15 Another embodiment is directed to fragments of a PRO1344 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 158 (SEQ ID NO:230).

20 In another embodiment, the invention provides isolated PRO1344 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1344 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 24 to about 720 of Figure 159 (SEQ ID NO:231).

25 In another aspect, the invention concerns an isolated PRO1344 polypeptide, comprising an amino acid sequence having at least about 80 % sequence identity, preferably at least about 85 % sequence identity, more preferably at least about 90 % sequence identity, most preferably at least about 95 % sequence identity to the sequence of amino acid residues 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231).

30 In a further aspect, the invention concerns an isolated PRO1344 polypeptide, comprising an amino acid sequence scoring at least about 80 % positives, preferably at least about 85 % positives, more preferably at least about 90 % positives, most preferably at least about 95 % positives when compared with the amino acid sequence of residues 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231).

35 In yet another aspect, the invention concerns an isolated PRO1344 polypeptide, comprising the sequence of amino acid residues 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231), or a fragment thereof sufficient to provide a binding site for an anti-PRO1344 antibody. Preferably, the PRO1344 fragment retains a qualitative biological activity of a native PRO1344 polypeptide.



In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1344 polypeptide having the sequence of amino acid residues from about 1 or about 24 to about 720, inclusive of Figure 159 (SEQ ID NO:231), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1344 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1344 antibody.

10 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1344 polypeptide by contacting the native PRO1344 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1344 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

15

66. PRO1109

A cDNA clone (DNA58737-1473) has been identified, having homology to nucleic acid encoding  $\beta$ -1,4-galactosyltransferase, that encodes a novel polypeptide, designated in the present application as "PRO1109".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1109 polypeptide.

20

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1109 polypeptide having the sequence of amino acid residues from about 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236), or (b) the complement of the DNA molecule of (a).

25

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1109 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 119 or about 200 and about 1150, inclusive, of Figure 160 (SEQ ID NO:235). Preferably, hybridization occurs under stringent hybridization and wash conditions.

30

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203136 (DNA58737-1473) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203136 (DNA58737-1473).

35

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236), or (b) the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1109 polypeptide having the sequence of amino acid residues from 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence  
10 identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1109 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as  
15 extending from about amino acid position 1 to about amino acid position 27 in the sequence of Figure 161 (SEQ ID NO:236).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
20 amino acid sequence of residues 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1109 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
25 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 160 (SEQ ID NO:235).

In another embodiment, the invention provides isolated PRO1109 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1109 polypeptide, which in  
30 certain embodiments, includes an amino acid sequence comprising residues 1 or about 28 to about 344 of Figure 161 (SEQ ID NO:236).

In another aspect, the invention concerns an isolated PRO1109 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the  
35 sequence of amino acid residues 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236).

In a further aspect, the invention concerns an isolated PRO1109 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least

about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236).

In yet another aspect, the invention concerns an isolated PRO1109 polypeptide, comprising the sequence of amino acid residues 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236), or a fragment thereof sufficient to provide a binding site for an anti-PRO1109 antibody. Preferably, the PRO1109 fragment  
5 retains a qualitative biological activity of a native PRO1109 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1109 polypeptide having the sequence of amino acid residues from about 1 or about 28 to about 344, inclusive of Figure 161 (SEQ ID NO:236), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about  
10 an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1109  
15 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1109 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1109 polypeptide by contacting the native PRO1109 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1109 polypeptide,  
20 or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 67. PRO1383

A cDNA clone (DNA58743-1609) has been identified, having homology to nucleic acid encoding the human melanoma cell-expressed protein nmb, that encodes a novel polypeptide, designated in the present  
25 application as "PRO1383".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1383 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most  
30 preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1383 polypeptide having the sequence of amino acid residues from about 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1383 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 122  
35 or about 194 and about 1390, inclusive, of Figure 162 (SEQ ID NO:240). Preferably, hybridization occurs under stringent hybridization and wash conditions.



In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203154 (DNA58743-1609) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the  
5 nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203154 (DNA58743-1609).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
10 identity to the sequence of amino acid residues 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1383 polypeptide having the sequence of amino acid residues from 1 or about 25 to  
15 about 423, inclusive of Figure 163 (SEQ ID NO:241), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding  
20 a PRO1383 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 24 in the sequence of Figure 163 (SEQ ID NO:241). The transmembrane domain has been tentatively identified as extending from about amino acid position 339 to about amino acid  
25 position 362 in the PRO1383 amino acid sequence (Figure 163, SEQ ID NO:241).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241), or (b)  
30 the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1383 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived  
35 from the nucleotide sequence shown in Figure 162 (SEQ ID NO:240).

In another embodiment, the invention provides isolated PRO1383 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.



In a specific aspect, the invention provides isolated native sequence PRO1383 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 25 to about 423 of Figure 163 (SEQ ID NO:241).

5 In another aspect, the invention concerns an isolated PRO1383 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241).

10 In a further aspect, the invention concerns an isolated PRO1383 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241).

In yet another aspect, the invention concerns an isolated PRO1383 polypeptide, comprising the sequence of amino acid residues 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241), or a fragment thereof sufficient to provide a binding site for an anti-PRO1383 antibody. Preferably, the PRO1383 fragment retains a qualitative biological activity of a native PRO1383 polypeptide.

15 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1383 polypeptide having the sequence of amino acid residues from about 1 or about 25 to about 423, inclusive of Figure 163 (SEQ ID NO:241), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a  
20 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1383 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1383 antibody.

25 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1383 polypeptide by contacting the native PRO1383 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1383 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.  
30

#### 68. PRO1003

Applicants have identified a cDNA clone, DNA58846-1409, that encodes a novel secreted polypeptide wherein the polypeptide is designated in the present application as "PRO1003".

35 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1003 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most

preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1003 polypeptide having the sequence of amino acid residues from 1 or about 25 to about 84, inclusive of Figure 165 (SEQ ID NO:246), or (b) the complement of the DNA molecule of (a).

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1003 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid between about residues 41 or about 113 and about 292 inclusive of Figure 164 (SEQ ID NO:245). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209957 (DNA58846-1409), which was deposited on June 9, 1998. In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209957 (DNA58846-1409).

15 In an additional aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to about 84, inclusive of Figure 165 (SEQ ID NO:246).

20 In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 84, inclusive of Figure 165 (SEQ ID NO:246).

25 Another embodiment is directed to fragments of a PRO1003 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1003 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

30 In a specific aspect, the invention provides isolated native sequence PRO1003 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 25 to 84 of Figure 165 (SEQ ID NO:246).

35 In another aspect, the invention concerns an isolated PRO1003 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to 84, inclusive of Figure 165 (SEQ ID NO:246).

In a further aspect, the invention concerns an isolated PRO1003 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least

about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 84 of Figure 165 (SEQ ID NO:246).

In yet another aspect, the invention concerns an isolated PRO1003 polypeptide, comprising the sequence of amino acid residues 1 or about 25 to about 84, inclusive of Figure 165 (SEQ ID NO:246), or a fragment thereof sufficient to provide a binding site for an anti-PRO1003 antibody. Preferably, the PRO1003 fragment  
5 retains a qualitative biological activity of a native PRO1003 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1003 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

#### 69. PRO1108

10 Applicants have identified a cDNA clone (DNA58848-1472) having homology to nucleic acid encoding the LPAAT protein that encodes a novel polypeptide, designated in the present application as "PRO1108".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1108 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1108 polypeptide having the sequence of amino acid residues from about 1 to about 456, inclusive of Figure 167 (SEQ ID NO:248), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1108 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 77 and about 1444, inclusive, of Figure 166 (SEQ ID NO:247). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209955 (DNA58848-1472). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209955 (DNA58848-1472).

30 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 456, inclusive of Figure 167 (SEQ ID NO:248).

35 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1108 polypeptide, with or without the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domains have been tentatively identified as being type II domains extending from about amino acid position 22 to about amino acid position 42, from about amino acid position 156 to about amino acid position 176, from



about amino acid position 180 to about amino acid position 199 and from about amino acid position 369 to about amino acid position 388 in the PRO1108 amino acid sequence (Figure 167, SEQ ID NO:248).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 456, inclusive of Figure 167 (SEQ ID NO:248).

Another embodiment is directed to fragments of a PRO1108 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

10 In another embodiment, the invention provides isolated PRO1108 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1108 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to about 456 of Figure 167 (SEQ ID NO:248).

15 In another aspect, the invention concerns an isolated PRO1108 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 456, inclusive of Figure 167 (SEQ ID NO:248).

20 In a further aspect, the invention concerns an isolated PRO1108 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 456, inclusive of Figure 167 (SEQ ID NO:248).

25 In yet another aspect, the invention concerns an isolated PRO1108 polypeptide, comprising the sequence of amino acid residues 1 to about 456, inclusive of Figure 167 (SEQ ID NO:248), or a fragment thereof sufficient to provide a binding site for an anti-PRO1108 antibody. Preferably, the PRO1108 fragment retains a qualitative biological activity of a native PRO1108 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1108 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

30 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1108 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1108 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1108 polypeptide.

In still a further embodiment, the invention concerns a composition comprising a PRO1108 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

35



**70. PRO1137**

Applicants have identified a cDNA clone, DNA58849-1494, that encodes a novel polypeptide having homology to ribosyltransferase wherein the polypeptide is designated in the present application as "PRO1137".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1137 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1137 polypeptide having the sequence of amino acid residues from 1 or about 15 to about 240, inclusive of Figure 169 (SEQ ID NO:250), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1137 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence having about residues 77 or about 119 to about 796, inclusive of Figure 168 (SEQ ID NO:249). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209958 (DNA58849-1494), which was deposited on June 9, 1998, or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide  
20 encoded by the human protein cDNA in ATCC Deposit No. 209958 (DNA58849-1494).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 15 to about 240, inclusive of Figure 169 (SEQ ID  
25 NO:250).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1137 polypeptide with or without the N-terminal signal sequence and/or the initiating methionine, or the complement of such encoding DNA molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 14 in the sequence of Figure 169 (SEQ ID  
30 NO:250).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, and most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 15 to about 240, inclusive of Figure 169 (SEQ ID NO:250).

35 Another embodiment is directed to fragments of a PRO1137 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50

nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1137 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

5 In a specific aspect, the invention provides isolated native sequence PRO1137 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 15 to 240 of Figure 169 (SEQ ID NO:250).

In another aspect, the invention concerns an isolated PRO1137 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 15 to 240, inclusive of Figure 169 (SEQ ID NO:250).

10 In a further aspect, the invention concerns an isolated PRO1137 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, and most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 15 to about 240 of Figure 169 (SEQ ID NO:250).

15 In yet another aspect, the invention concerns an isolated PRO1137 polypeptide, comprising the sequence of amino acid residues 1 or about 15 to about 240, inclusive of Figure 169 (SEQ ID NO:250), or a fragment thereof sufficient to provide a binding site for an anti-PRO1137 antibody. Preferably, the PRO1137 fragment retains a qualitative biological activity of a native PRO1137 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1137 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

20 In yet another embodiment, the invention concerns agonist and antagonists of the PRO1137 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1137 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1137 polypeptide.

25 In still a further embodiment, the invention concerns a composition comprising a PRO1137 polypeptide as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 71. PRO1138

Applicants have identified a cDNA clone, DNA58850-1495, that encodes a novel polypeptide having homology to CD84 leukocyte antigen wherein the polypeptide is designated in the present application as  
30 "PRO1138".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1138 polypeptide.

35 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1138 polypeptide having the sequence of amino acid residues from 1 or about 23 to about 335, inclusive of Figure 171 (SEQ ID NO:253), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1138 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence having about residues 38 or about 104 to about 1042, inclusive of Figure 170 (SEQ ID NO:252). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209956 (DNA58850-1495), which was deposited on June 9, 1998, or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide  
10 encoded by the human protein cDNA in ATCC Deposit No. 209956 (DNA58850-1495).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 to about 335, inclusive of Figure 171 (SEQ ID  
15 NO:253).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1138 extracellular domain (ECD), with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble variants (i.e. transmembrane domain(s) deleted or inactivated) or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from  
20 amino acid position 1 to about amino acid position 22 in the sequence of Figure 171 (SEQ ID NO:253). A transmembrane domain region has been tentatively identified as extending from about amino acid position 224 to about amino acid position 250 in the PRO1138 amino acid sequence (Figure 171, SEQ ID NO:253).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, and most preferably  
25 at least about 95% positives when compared with the amino acid sequence of residues 1 or about 23 to about 335, inclusive of Figure 171 (SEQ ID NO:253).

Another embodiment is directed to fragments of a PRO1138 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
30 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1138 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1138 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 23 to 335 of Figure 171 (SEQ ID  
35 NO:253).

In another aspect, the invention concerns an isolated PRO1138 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more



preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 to 335, inclusive of Figure 171 (SEQ ID NO:253).

5 In a further aspect, the invention concerns an isolated PRO1138 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, and most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 23 to about 335 of Figure 171 (SEQ ID NO:253).

10 In another aspect, the invention concerns a PRO1138 extracellular domain comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 to X of Figure 171 (SEQ ID NO:253), wherein X is any one of amino acid residues 219 to 228 of Figure 171 (SEQ ID NO:253).

In yet another aspect, the invention concerns an isolated PRO1138 polypeptide, comprising the sequence of amino acid residues 1 or about 23 to about 335, inclusive of Figure 171 (SEQ ID NO:253), or a fragment thereof sufficient to provide a binding site for an anti-PRO1138 antibody. Preferably, the PRO1138 fragment retains a qualitative biological activity of a native PRO1138 polypeptide.

15 In another aspect, the present invention is directed to fragments of a PRO1138 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

In yet another embodiment, the invention concerns agonist and antagonists of the PRO1138 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1138 antibody.

20 In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1138 polypeptide.

In still a further embodiment, the invention concerns a composition comprising a PRO1138 polypeptide as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

25 In another embodiment, the invention provides a nucleotide sequence designated herein as DNA49140 comprising the nucleotide sequence of Figure 172 (SEQ ID NO:254).

## 72. PRO1054

A cDNA clone (DNA58853-1423) has been identified, having homology to nucleic acid encoding major urinary proteins (MUPs) that encodes a novel polypeptide, designated in the present application as "PRO1054".

30 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1054 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1054 polypeptide having the sequence of amino acid residues from about 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1054 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 46



or about 100 and about 585, inclusive, of Figure 173 (SEQ ID NO:255). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule  
5 encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203016 (DNA58853-1423) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203016 (DNA58853-1423).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA  
10 encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10  
15 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1054 polypeptide having the sequence of amino acid residues from 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence  
20 identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1054 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 18 in the sequence of Figure 174 (SEQ  
25 ID NO:256).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256), or (b)  
30 the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1054 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived  
35 from the nucleotide sequence shown in Figure 173 (SEQ ID NO:255).

In another embodiment, the invention provides isolated PRO1054 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1054 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 19 to about 180 of Figure 174 (SEQ ID NO:256).

5 In another aspect, the invention concerns an isolated PRO1054 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256).

10 In a further aspect, the invention concerns an isolated PRO1054 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256).

In yet another aspect, the invention concerns an isolated PRO1054 polypeptide, comprising the sequence of amino acid residues 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256), or a fragment thereof sufficient to provide a binding site for an anti-PRO1054 antibody. Preferably, the PRO1054 fragment retains a qualitative biological activity of a native PRO1054 polypeptide.

15 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1054 polypeptide having the sequence of amino acid residues from about 1 or about 19 to about 180, inclusive of Figure 174 (SEQ ID NO:256), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 20 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1054 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1054 antibody.

25 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1054 polypeptide by contacting the native PRO1054 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

30 In a still further embodiment, the invention concerns a composition comprising a PRO1054 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 73. PRO994

A cDNA clone (DNA58855-1422) has been identified, having homology to nucleic acid encoding the tumor-associated antigen L6 that encodes a novel polypeptide, designated in the present application as "PRO994".

35 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO994 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO994 polypeptide having the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258), or (b) the complement of the DNA molecule of (a).

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO994 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 31 and about 717, inclusive, of Figure 175 (SEQ ID NO:257). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203018 (DNA58855-1422) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
15 ATCC Deposit No. 203018 (DNA58855-1422).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258), or  
20 (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO994 polypeptide having the sequence of amino acid residues from 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258), or (b) the complement of the DNA molecule of (a), and, if the DNA  
25 molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO994 polypeptide, with or without the initiating methionine, and its soluble, i.e., transmembrane domain  
30 deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The multiple transmembrane domains have been tentatively identified as extending from about amino acid position 10 to about amino acid position 31, from about amino acid position 50 to about amino acid position 72, from about amino acid position 87 to about amino acid position 110 and from about amino acid position 191 to about amino acid position 213 in the PRO994 amino acid sequence (Figure 176, SEQ ID NO:258).

35 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the



amino acid sequence of residues 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO994 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
5 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 175 (SEQ ID NO:257).

In another embodiment, the invention provides isolated PRO994 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO994 polypeptide, which in  
10 certain embodiments, includes an amino acid sequence comprising residues 1 to about 229 of Figure 176 (SEQ ID NO:258).

In another aspect, the invention concerns an isolated PRO994 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the  
15 sequence of amino acid residues 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258).

In a further aspect, the invention concerns an isolated PRO994 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258).

20 In yet another aspect, the invention concerns an isolated PRO994 polypeptide, comprising the sequence of amino acid residues 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258), or a fragment thereof sufficient to provide a binding site for an anti-PRO994 antibody. Preferably, the PRO994 fragment retains a qualitative biological activity of a native PRO994 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA  
25 molecule under stringent conditions with (a) a DNA molecule encoding a PRO994 polypeptide having the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 176 (SEQ ID NO:258), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising  
30 the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO994 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO994 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a  
35 native PRO994 polypeptide by contacting the native PRO994 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.



In a still further embodiment, the invention concerns a composition comprising a PRO994 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**74. PRO812**

5 A cDNA clone (DNA59205-1421) has been identified, having homology to nucleic acid encoding prostatic steroid-binding protein c1 that encodes a novel polypeptide, designated in the present application as "PRO812".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO812 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO812 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO812 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 55 or about 100 and about 303, inclusive, of Figure 177 (SEQ ID NO:259). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203009 (DNA59205-1421) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203009 (DNA59205-1421).

25 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260), or (b) the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO812 polypeptide having the sequence of amino acid residues from 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO812 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 15 in the sequence of Figure 178 (SEQ ID NO:260).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO812 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 177 (SEQ ID NO:259).

15 In another embodiment, the invention provides isolated PRO812 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO812 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 16 to about 83 of Figure 178 (SEQ ID NO:260).

20 In another aspect, the invention concerns an isolated PRO812 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260).

25 In a further aspect, the invention concerns an isolated PRO812 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260).

30 In yet another aspect, the invention concerns an isolated PRO812 polypeptide, comprising the sequence of amino acid residues 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260), or a fragment thereof sufficient to provide a binding site for an anti-PRO812 antibody. Preferably, the PRO812 fragment retains a qualitative biological activity of a native PRO812 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO812 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 83, inclusive of Figure 178 (SEQ ID NO:260), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host

cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO812 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO812 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO812 polypeptide by contacting the native PRO812 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO812 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

10 75. PRO1069

Applicants have identified a cDNA clone, DNA59211-1450, that encodes a novel polypeptide having homology to CHIF wherein the polypeptide is designated in the present application as "PRO1069".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1069 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1069 polypeptide having the sequence of amino acid residues from 1 or about 17 to about 89, inclusive of Figure 180 (SEQ ID NO:262), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1069 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence having about residues 197 or about 245 to about 463, inclusive of Figure 179 (SEQ ID NO:261). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209960 (DNA59211-1450), which was deposited on June 9, 1998. In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in  
30 ATCC Deposit No. 209960 (DNA59211-1450).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to about 89, inclusive of Figure 180 (SEQ ID  
35 NO:262).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1069 extracellular domain (ECD), with or without the N-terminal signal sequence and/or the initiating



methionine, and its soluble variants (i.e. transmembrane domain(s) deleted or inactivated) or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 to about amino acid position 16 in the sequence of Figure 180 (SEQ ID NO:262). A transmembrane domain region has been tentatively identified as extending from about amino acid position 36 to about amino acid position 59 in the PRO1069 amino acid sequence (Figure 180, SEQ ID NO:262).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 17 to about 89, inclusive of Figure 180 (SEQ ID NO:262).

10 Another embodiment is directed to fragments of a PRO1069 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1069 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

15 In a specific aspect, the invention provides isolated native sequence PRO1069 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 17 to 89 of Figure 180 (SEQ ID NO:262).

20 In another aspect, the invention concerns an isolated PRO1069 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to 89, inclusive of Figure 180 (SEQ ID NO:262).

25 In a further aspect, the invention concerns an isolated PRO1069 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 17 to about 89 of Figure 180 (SEQ ID NO:262).

30 In another aspect, the invention concerns a PRO1069 extracellular domain comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to X of Figure 180 (SEQ ID NO:262), wherein X is any one of amino acid residues 32 to 41 of Figure 180 (SEQ ID NO:262).

In yet another aspect, the invention concerns an isolated PRO1069 polypeptide, comprising the sequence of amino acid residues 1 or about 17 to about 89, inclusive of Figure 180 (SEQ ID NO:262), or a fragment thereof sufficient to provide a binding site for an anti-PRO1069 antibody. Preferably, the PRO1069 fragment retains a qualitative biological activity of a native PRO1069 polypeptide.

35 In another aspect, the present invention is directed to fragments of a PRO1069 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.



In yet another embodiment, the invention concerns agonist and antagonists of the PRO1069 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1069 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1069 polypeptide.

5 In still a further embodiment, the invention concerns a composition comprising a PRO1069 polypeptide as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 76. PRO1129

Applicants have identified a cDNA clone (DNA59213-1487) having homology to nucleic acid encoding cytochrome P-450 family members that encodes a novel polypeptide, designated in the present application as  
10 "PRO1129".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1129 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most  
15 preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1129 polypeptide having the sequence of amino acid residues from about 1 to about 524, inclusive of Figure 182 (SEQ ID NO:264), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1129 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 42  
20 and about 1613, inclusive, of Figure 181 (SEQ ID NO:263). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule  
25 encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209959 (DNA59213-1487). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209959 (DNA59213-1487).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
30 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 524, inclusive of Figure 182 (SEQ ID NO:264).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1129 polypeptide, with or without the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The type II  
35 transmembrane domains have been tentatively identified as extending from about amino acid position 13 to about amino acid position 32 and from about amino acid position 77 to about amino acid position 102 in the PRO1129 amino acid sequence (Figure 182, SEQ ID NO:264).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 524, inclusive of Figure 182 (SEQ ID NO:264).

5 Another embodiment is directed to fragments of a PRO1129 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1129 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

10 In a specific aspect, the invention provides isolated native sequence PRO1129 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to about 524 of Figure 182 (SEQ ID NO:264).

In another aspect, the invention concerns an isolated PRO1129 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 524, inclusive of Figure 182 (SEQ ID NO:264).

15 In a further aspect, the invention concerns an isolated PRO1129 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 524, inclusive of Figure 182 (SEQ ID NO:264).

In yet another aspect, the invention concerns an isolated PRO1129 polypeptide, comprising the sequence of amino acid residues 1 to about 524, inclusive of Figure 182 (SEQ ID NO:264), or a fragment thereof sufficient to provide a binding site for an anti-PRO1129 antibody. Preferably, the PRO1129 fragment retains a qualitative biological activity of a native PRO1129 polypeptide.

25 In another aspect, the present invention is directed to fragments of a PRO1129 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1129 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1129 antibody.

30 In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1129 polypeptide.

In still a further embodiment, the invention concerns a composition comprising a PRO1129 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 77. PRO1068

35 A cDNA clone (DNA59214-1449) has been identified, that encodes a novel polypeptide having homology to urotensin and designated the present application as "PRO1068."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1068 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1068 polypeptide having the sequence of amino acid residues from about 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1068 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 102 and about 413, inclusive, of Figure 183 (SEQ ID NO:265). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203046 (DNA59214-1449), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203046 (DNA59214-1449).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1068 polypeptide having the sequence of amino acid residues from about 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1068 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 20 in the sequence of Figure 184 (SEQ ID NO:266).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the



amino acid sequence of residues 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1068 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1068 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1068 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 21 to 124 of Figure 184 (SEQ ID NO:266).

In another aspect, the invention concerns an isolated PRO1068 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266).

In a further aspect, the invention concerns an isolated PRO1068 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 21 to 124 of Figure 184 (SEQ ID NO:266).

In yet another aspect, the invention concerns an isolated PRO1068 polypeptide, comprising the sequence of amino acid residues 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266), or a fragment thereof sufficient to provide a binding site for an anti-PRO1068 antibody. Preferably, the PRO1068 fragment retains a qualitative biological activity of a native PRO1068 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1068 polypeptide having the sequence of amino acid residues from about 21 to about 124, inclusive of Figure 184 (SEQ ID NO:266), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1068 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1068 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1068 polypeptide, by contacting the native PRO1068 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1068 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.



**78. PRO1066**

Applicants have identified a cDNA clone (DNA59215-1425) that encodes a novel secreted polypeptide, designated in the present application as "PRO1066".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1066 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1066 polypeptide having the sequence of amino acid residues from about 1 or about 24 to about 117, inclusive of Figure 186 (SEQ ID NO:268), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1066 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 176 or about 245 and about 527, inclusive, of Figure 185 (SEQ ID NO:267). Preferably, hybridization occurs under stringent hybridization and wash conditions.

15 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209961 (DNA59215-1425). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209961 (DNA59215-1425).

20 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 117, inclusive of Figure 186 (SEQ ID NO:268).

25 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1066 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 23 in the sequence of Figure 186 (SEQ ID NO:268).

30 In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 24 to about 117, inclusive of Figure 186 (SEQ ID NO:268).

35 Another embodiment is directed to fragments of a PRO1066 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1066 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1066 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 24 to about 117 of Figure 186 (SEQ ID NO:268).

5 In another aspect, the invention concerns an isolated PRO1066 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 24 to about 117, inclusive of Figure 186 (SEQ ID NO:268).

10 In a further aspect, the invention concerns an isolated PRO1066 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 24 to about 117, inclusive of Figure 186 (SEQ ID NO:268).

15 In yet another aspect, the invention concerns an isolated PRO1066 polypeptide, comprising the sequence of amino acid residues 1 or about 24 to about 117, inclusive of Figure 186 (SEQ ID NO:268), or a fragment thereof sufficient to provide a binding site for an anti-PRO1066 antibody. Preferably, the PRO1066 fragment retains a qualitative biological activity of a native PRO1066 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1066 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

## 20 79. PRO1184

Applicants have identified a cDNA clone (DNA59220-1514) that encodes a novel secreted polypeptide, designated in the present application as "PRO1184".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1184 polypeptide.

25 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1184 polypeptide having the sequence of amino acid residues from 1 or about 39 through 142 of Figure 188 (SEQ ID NO:270), or (b) the complement of the DNA molecule of (a).

30 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1184 polypeptide comprising DNA hybridizing to the complement of the nucleic acid at about residues 106 or 220 through 531 of SEQ ID NO:269. In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1184 polypeptide comprising DNA hybridizing to the complement of the nucleic of SEQ ID NO:269. Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule

encoding the same mature polypeptide encoded by the human protein cDNA in ATCC of DNA59220-1514. In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit of DNA59220-1514.

5 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 39 through 142 of SEQ ID NO:270.

10 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1184 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble variants, or is complementary to such an encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 to about amino acid position 38 of SEQ ID NO:270.

15 In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 39 through 142 of SEQ ID NO:270.

Another embodiment is directed to fragments of a PRO1184 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length.

20 In another embodiment, the invention provides isolated PRO1184 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1184 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 39 through 142 of SEQ ID NO:270.

25 In another aspect, the invention concerns an isolated PRO1184 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 39 through 142 of SEQ ID NO:270.

30 In a further aspect, the invention concerns an isolated PRO1184 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 39 through 142 of SEQ ID NO:270.

35 In yet another aspect, the invention concerns an isolated PRO1184 polypeptide, comprising the sequence of amino acid residues 1 or about 39 through 142 of SEQ ID NO:270, or a fragment thereof sufficient to provide a binding site for an anti-PRO1184 antibody. Preferably, the PRO1184 fragment retains a qualitative biological activity of a native PRO1184 polypeptide.

In another aspect, the present invention is directed to fragments of a PRO1184 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

**80. PRO1360**

5 A cDNA clone (DNA59488-1603) has been identified that encodes a novel polypeptide designated in the present application as "PRO1360."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1360 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1360 polypeptide having the sequence of amino acid residues from about 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1360 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 140 and about 908, inclusive, of Figure 189 (SEQ ID NO:271). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203157 (DNA59488-1603), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203157 (DNA59488-1603).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1360 polypeptide having the sequence of amino acid residues from about 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more



preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1360 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1360 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1360 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 30 through 285 of Figure 190 (SEQ ID NO:272).

In another aspect, the invention concerns an isolated PRO1360 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272).

In a further aspect, the invention concerns an isolated PRO1360 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 30 through 285 of Figure 190 (SEQ ID NO:272).

In yet another aspect, the invention concerns an isolated PRO1360 polypeptide, comprising the sequence of amino acid residues 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272), or a fragment thereof sufficient to provide a binding site for an anti-PRO1360 antibody. Preferably, the PRO1360 fragment retains a qualitative biological activity of a native PRO1360 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1360 polypeptide having the sequence of amino acid residues from about 30 to about 285, inclusive of Figure 190 (SEQ ID NO:272), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1360 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1360 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1360 polypeptide, by contacting the native PRO1360 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1360 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**81. PRO1029**

A cDNA clone (DNA59493-1420) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1029".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1029 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1029 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1029 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 39 or about 96 and about 296, inclusive, of Figure 191 (SEQ ID NO:274). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203050 (DNA59493-1420) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203050 (DNA59493-1420).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1029 polypeptide having the sequence of amino acid residues from 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1029 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is

complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 19 in the sequence of Figure 192 (SEQ ID NO:274).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO1029 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 191 (SEQ ID NO:273).

In another embodiment, the invention provides isolated PRO1029 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

15 In a specific aspect, the invention provides isolated native sequence PRO1029 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 20 to about 86 of Figure 192 (SEQ ID NO:274).

20 In another aspect, the invention concerns an isolated PRO1029 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274).

25 In a further aspect, the invention concerns an isolated PRO1029 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274).

In yet another aspect, the invention concerns an isolated PRO1029 polypeptide, comprising the sequence of amino acid residues 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274), or a fragment thereof sufficient to provide a binding site for an anti-PRO1029 antibody. Preferably, the PRO1029 fragment retains a qualitative biological activity of a native PRO1029 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1029 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 86, inclusive of Figure 192 (SEQ ID NO:274), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

**82.     PRO1139**

Applicants have identified a novel cDNA clone (DNA59497-1496) that encodes a novel human protein originally designated as PRO1139.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1139 polypeptide having the sequence of amino acid residues from about 29 to about 131 of Figure 194 (SEQ ID NO:276), or (b) the complement of the DNA molecule of (a).

In another embodiment, the invention concerns an isolated nucleic acid molecule comprising DNA hybridizing to the complement of the polynucleotide sequence between about residues 80 and 391, inclusive, of Figure 193 (SEQ ID NO:275). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further embodiment, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209941 (DNA59497-1496). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209941 (DNA59497-1496).

In a still further embodiment, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 29 to about 131 of Figure 194 (SEQ ID NO:276).

In a specific embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a native or variant PRO1139 polypeptide, with or without the N-terminal signal sequence, and with or without the transmembrane regions which have been identified as stretching from about amino acid position 33 to about amino acid position 52; from about amino acid position 71 to about amino acid position 89; and from about amino acid position 98 to about amino acid position 120, respectively of the amino acid sequence of Figure 194, SEQ ID NO:276. In one aspect, the isolated nucleic acid comprises DNA encoding a mature, full-length native PRO1139 polypeptide having amino acid residues 1 to 131 of Figure 194, SEQ ID NO:276, or is complementary to such encoding nucleic acid sequence.

In another embodiment, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues from about 29 to about 131 of Figure 194 (SEQ ID NO:276).

In another embodiment, the invention provides isolated PRO1139 polypeptides. In particular, the invention provides isolated native sequence PRO1139 polypeptide, which in one embodiment, include the amino acid sequence comprising residues 29 to 131 of Figure 194 (SEQ ID NO:276). The invention also provides for variants of the PRO1139 polypeptide which are encoded by any of the isolated nucleic acid molecules



hereinabove defined. Specific variants include, but are not limited to, deletion (truncated) variants of the full-length native sequence PRO1139 which lack the N-terminal signal sequence and/or have at least one transmembrane domain deleted or inactivated. The variants specifically include variants of the full-length mature polypeptide of Figure 194 (SEQ ID NO:276) in which one or more of the transmembrane regions between amino acid residues 33-52, 71-8, and 98-120, respectively have been deleted or inactivated, and which may additionally have the N-terminal signal sequence (amino acid residues 1-28) and/or the initiating methionine deleted.

In a further embodiment, the invention concerns an isolated PRO1139 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues from about 29 to about 131 of Figure 194 (SEQ ID NO:276).

In yet another aspect, the invention concerns an isolated PRO1139 polypeptide, comprising the sequence of amino acid residues 29 to about 131, inclusive of Figure 194 (SEQ ID NO:276) or a fragment thereof sufficient to provide a binding site for an anti-PRO1139 antibody. Preferably, the PRO1139 fragment retains a qualitative biological activity of a native PRO1139 polypeptide.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1139 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1139 antibody.

In a further embodiment, the invention concerns screening assays to identify agonists or antagonists of a native PRO1139 polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1139 polypeptide (including variants), or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

The invention also concerns a method of treating obesity comprising administering to a patient an effective amount of an antagonist of a PRO1139 polypeptide. In a specific embodiment, the antagonist is a blocking antibody specifically binding a native PRO1139 polypeptide.

### 83. PRO1309

A cDNA clone (DNA59588-1571) has been identified that encodes a novel polypeptide having leucine rich repeats and designated in the present application as "PRO1309."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1309 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1309 polypeptide having the sequence of amino acid residues from about 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1309 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 822 and about 2285, inclusive, of Figure 195 (SEQ ID NO:277). Preferably, hybridization occurs under stringent

hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203106 (DNA59588-1571), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203106 (DNA59588-1571).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1309 polypeptide having the sequence of amino acid residues from about 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1309 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 34 in the sequence of Figure 196 (SEQ ID NO:278). The transmembrane domain has been tentatively identified as extending from about amino acid position 428 through about amino acid position 450 in the PRO1309 amino acid sequence (Figure 196, SEQ ID NO:278).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1309 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1309 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1309 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 35 through 522 of Figure 196 (SEQ ID NO:278).

5 In another aspect, the invention concerns an isolated PRO1309 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278).

10 In a further aspect, the invention concerns an isolated PRO1309 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 35 through 522 of Figure 196 (SEQ ID NO:278).

In yet another aspect, the invention concerns an isolated PRO1309 polypeptide, comprising the sequence of amino acid residues 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278), or a fragment thereof sufficient to provide a binding site for an anti-PRO1309 antibody. Preferably, the PRO1309 fragment retains a qualitative biological activity of a native PRO1309 polypeptide.

15 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1309 polypeptide having the sequence of amino acid residues from about 35 to about 522, inclusive of Figure 196 (SEQ ID NO:278), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1309 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1309 antibody.

25 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1309 polypeptide, by contacting the native PRO1309 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1309 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

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#### 84. PRO1028

Applicants have identified a cDNA clone that encodes a secreted novel polypeptide, wherein the polypeptide is designated in the present application as "PRO1028".

35 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1028 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1028 polypeptide having amino acid residues 1 through 197 of Figure 198 (SEQ ID NO:281), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally,

under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the vector deposited on June 9, 1998 with the ATCC as DNA59603-1419 which includes the nucleotide sequence encoding PRO1028.

In another embodiment, the invention provides isolated PRO1028 polypeptide. In particular, the invention provides isolated native sequence PRO1028 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 197 of Figure 198 (SEQ ID NO:281). Optionally, the PRO1028 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the vector deposited on June 9, 1998 with the ATCC as DNA59603-1419.

#### 85. PRO1027

A cDNA clone (DNA59605-1418) has been identified, having a type II fibronectin collagen-binding domain that encodes a novel polypeptide, designated in the present application as "PRO1027."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1027 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1027 polypeptide having the sequence of amino acid residues from about 1 or 34 to about 77, inclusive of Figure 200 (SEQ ID NO:283), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-77, or in another embodiment, 34-77.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1027 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 31 or 130 and about 261, inclusive, of Figure 199 (SEQ ID NO:282). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203005 (DNA59605-1418), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203005 (DNA59605-1418).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 34 to about 77, inclusive of Figure 200 (SEQ ID NO:283), or the complement of the DNA of (a).



In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1027 polypeptide having the sequence of amino acid residues from about 1 or 34 to about 77, inclusive of Figure 200 (SEQ ID NO:283), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 34 to about 77, inclusive of Figure 200 (SEQ ID NO:283), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1027 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1027 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 34 through 77 of Figure 200 (SEQ ID NO:283).

In another aspect, the invention concerns an isolated PRO1027 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 34 to about 77, inclusive of Figure 200 (SEQ ID NO:283).

In a further aspect, the invention concerns an isolated PRO1027 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 34 through 77 of Figure 200 (SEQ ID NO:283).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1027 polypeptide having the sequence of amino acid residues from about 1 or 34 to about 77, inclusive of Figure 200 (SEQ ID NO:283), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1027 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1027 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1027 polypeptide, by contacting the native PRO1027 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1027 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

86. **PRO1107**

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with PC-1, wherein the polypeptide is designated in the present application as "PRO1107".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1107 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1107 polypeptide having amino acid residues 1 through 477 of Figure 202 (SEQ ID NO:285), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1107 polypeptide having amino acid residues about 23 through 477 of Figure 202 (SEQ ID NO:285) or amino acids about 1 or 23 through 428  $\pm$  5 of Figure 202 (SEQ ID NO:285), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA59606-1471 vector deposited on June 9, 1998 with the ATCC, which includes the nucleotide sequence encoding PRO1107.

In another embodiment, the invention provides isolated PRO1107 polypeptide. In particular, the invention provides isolated native sequence PRO1107 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 477 of Figure 202 (SEQ ID NO:285). Additional embodiments of the present invention are directed to PRO1107 polypeptides comprising amino acids about 23 through 477 of Figure 202 (SEQ ID NO:285) or amino acids about 1 or 23 through 428  $\pm$  5 of Figure 202 (SEQ ID NO:285). Optionally, the PRO1107 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA59606-1471 vector deposited with the ATCC on June 9, 1998.

87. **PRO1140**

Applicants have identified a cDNA clone, DNA59607-1497, that encodes a novel multi-span transmembrane polypeptide wherein the polypeptide is designated in the present application as "PRO1140".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1140 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1140 polypeptide having the sequence of amino acid residues from 1 to about 255, inclusive of Figure 204 (SEQ ID NO:287), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1140 polypeptide comprising DNA that hybridizes to the complement of the nucleic acid sequence having about residues 210 to about 974, inclusive of Figure 203 (SEQ ID NO:286). Preferably, hybridization occurs under

stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209946 (DNA59607-1497), which was deposited on June 9, 1998, or (b) the complement of the DNA molecule of (a).  
5 In a preferred embodiment, the nucleic acid comprises a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209946 (DNA59607-1497).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
10 identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 255, inclusive of Figure 204 (SEQ ID NO:287).

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1140 extracellular domain (ECD), with or without the initiating methionine, and its soluble variants (i.e. transmembrane domain(s) deleted or inactivated) or is complementary to such encoding nucleic acid molecule.  
15 Referring to the PRO1140 amino acid sequence (SEQ ID NO:287) shown in Figure 204, transmembrane domain regions have been tentatively identified as extending from about amino acid positions 101 to about 118, about 141 to about 161, and from about 172 to about 191.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 90% positives, and most preferably  
20 at least about 95% positives when compared with the amino acid sequence of residues 1 to about 255, inclusive of Figure 204 (SEQ ID NO:287).

Another embodiment is directed to fragments of a PRO1140 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
25 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1140 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1140 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 255 of Figure 204 (SEQ ID NO:287).

30 In another aspect, the invention concerns an isolated PRO1140 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to 255, inclusive of Figure 204 (SEQ ID NO:287).

In a further aspect, the invention concerns an isolated PRO1140 polypeptide, comprising an amino acid  
35 sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, and most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 255 of Figure 204 (SEQ ID NO:287).

In another aspect, the invention concerns a PRO1140 extracellular domain comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, and most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to X of Figure 204 (SEQ ID NO:287), wherein X is any one of amino acid residues 96 to 105 of Figure 204 (SEQ ID NO:287).

5 In yet another aspect, the invention concerns an isolated PRO1140 polypeptide, comprising the sequence of amino acid residues 1 to about 255, inclusive of Figure 204 (SEQ ID NO:287), or a fragment thereof sufficient to provide a binding site for an anti-PRO1140 antibody. Preferably, the PRO1140 fragment retains a qualitative biological activity of a native PRO1140 polypeptide.

10 In another aspect, the present invention is directed to fragments of a PRO1140 polypeptide which are sufficiently long to provide an epitope against which an antibody may be generated.

#### 88. PRO1106

Applicants have identified a cDNA clone that encodes a novel polypeptide having sequence identity with a peroxisomal calcium-dependent solute carrier, wherein the polypeptide is designated in the present application as "PRO1106".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1106 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1106 polypeptide having amino acid residues 1 through 469 of Figure 206 (SEQ ID NO:289), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, 20 under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA59609-1470 vector deposited on June 9, 1998 with the ATCC, which includes the nucleotide sequence encoding PRO1106.

25 In another embodiment, the invention provides isolated PRO1106 polypeptide. In particular, the invention provides isolated native sequence PRO1106 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 469 of Figure 206 (SEQ ID NO:289). Optionally, the PRO1106 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA59609-1470 vector deposited with the ATCC on June 9, 1998.

#### 89. PRO1291

30 A cDNA clone (DNA59610-1556) has been identified, having homology to nucleic acid encoding butyrophilin that encodes a novel polypeptide, designated in the present application as "PRO1291".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1291 polypeptide.

35 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1291 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID



NO:291), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1291 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 61 or about 145 and about 906, inclusive, of Figure 207 (SEQ ID NO:290). Preferably, hybridization occurs under stringent hybridization and wash conditions.

5 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209990 (DNA59610-1556) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the  
10 nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209990 (DNA59610-1556).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
15 identity to the sequence of amino acid residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1291 polypeptide having the sequence of amino acid residues from 1 or about 29 to  
20 about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding  
25 a PRO1291 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 28 in the sequence of Figure 208 (SEQ ID NO:291). The transmembrane domain has been tentatively identified as extending from about amino acid position 258 to about amino acid  
30 position 281 in the PRO1291 amino acid sequence (Figure 208, SEQ ID NO:291).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b)  
35 the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1291 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length,

preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 207 (SEQ ID NO:290).

In another embodiment, the invention provides isolated PRO1291 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

5 In a specific aspect, the invention provides isolated native sequence PRO1291 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 29 to about 282 of Figure 208 (SEQ ID NO:291).

10 In another aspect, the invention concerns an isolated PRO1291 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291).

15 In a further aspect, the invention concerns an isolated PRO1291 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291).

In yet another aspect, the invention concerns an isolated PRO1291 polypeptide, comprising the sequence of amino acid residues 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or a fragment thereof sufficient to provide a binding site for an anti-PRO1291 antibody. Preferably, the PRO1291 fragment retains a qualitative biological activity of a native PRO1291 polypeptide.

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1291 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 282, inclusive of Figure 208 (SEQ ID NO:291), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a  
25 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1291 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1291 antibody.

30 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1291 polypeptide by contacting the native PRO1291 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1291 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

35

**90.     PRO1105**

Applicants have identified a cDNA clone that encodes a novel polypeptide having two transmembrane domains, wherein the polypeptide is designated in the present application as "PRO1105".

5     In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1105 polypeptide. In one aspect, the isolated nucleic acid comprises DNA encoding the PRO1105 polypeptide having amino acid residues 1 through 180 of Figure 210 (SEQ ID NO:293), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. In other aspects, the isolated nucleic acid comprises DNA encoding the PRO1105 polypeptide having amino acid residues about 20 through 180 of Figure 210 (SEQ ID NO:293), or is complementary to such encoding nucleic acid sequence, and remains stably bound to it under at least moderate, and optionally, under high stringency conditions. The isolated nucleic acid sequence may comprise the cDNA insert of the DNA59612-1466 vector deposited on June 9, 1998 with the ATCC, which includes the nucleotide sequence encoding PRO1105.

15     In another embodiment, the invention provides isolated PRO1105 polypeptide. In particular, the invention provides isolated native sequence PRO1105 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 180 of Figure 210 (SEQ ID NO:293). Additional embodiments of the present invention are directed to PRO1105 polypeptides comprising amino acids about 20 through 180 of Figure 210 (SEQ ID NO:293). Other embodiments of the present invention are directed to PRO1105 polypeptides comprising amino acids about 1 through 79 and 100 through about 144 of Figure 210 (SEQ ID NO:293). Optionally, the PRO1105 polypeptide is obtained or is obtainable by expressing the polypeptide encoded by the cDNA insert of the DNA59612-1466 vector deposited with the ATCC on June 9, 1998.

**91.     PRO511**

A cDNA clone (DNA59613-1417) has been identified, having some sequence identity with RoBo-1 and phospholipase inhibitors that encodes a novel polypeptide, designated in the present application as "PRO1026."

25     In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1026 polypeptide.

30     In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1026 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 237, inclusive of Figure 212 (SEQ ID NO:295), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-237, or in another embodiment, 26-237.

35     In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1026 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 233 or 308 and about 943, inclusive, of Figure 212 (SEQ ID NO:295). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203007 (DNA59613-1417), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203007 (DNA59613-1417).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 26 to about 237, inclusive of Figure 212 (SEQ ID NO:295), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1026 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 237, inclusive of Figure 212 (SEQ ID NO:295), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 26 to about 237, inclusive of Figure 212 (SEQ ID NO:295), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1026 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1026 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 26 through 237 of Figure 212 (SEQ ID NO:295).

In another aspect, the invention concerns an isolated PRO1026 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 26 to about 237, inclusive of Figure 212 (SEQ ID NO:295).

In a further aspect, the invention concerns an isolated PRO1026 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 26 through 237 of Figure 212 (SEQ ID NO:295).



In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1026 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 237, inclusive of Figure 212 (SEQ ID NO:295), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1026 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1026 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1026 polypeptide, by contacting the native PRO1026 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1026 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

## 92. PRO1104

A cDNA clone (DNA59616-1465) has been identified, that encodes a novel polypeptide, designated in the present application as "PRO1104."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1104 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1104 polypeptide having the sequence of amino acid residues from about 1 or about 23 to about 341, inclusive of Figure 214 (SEQ ID NO:297), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-341, or in another embodiment, 23-341.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1104 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 109 or 175 and about 1131, inclusive, of Figure 213 (SEQ ID NO:296). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209991 (DNA59616-1465), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC

Deposit No. 209991 (DNA59616-1465).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or about 23 to about 341, inclusive of Figure 214 (SEQ ID NO:297), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1104 polypeptide having the sequence of amino acid residues from about 1 or about 23 to about 341, inclusive of Figure 214 (SEQ ID NO:297), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 23 to about 341, inclusive of Figure 214 (SEQ ID NO:297), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1104 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1104 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or about 23 through 341 of Figure 214 (SEQ ID NO:297).

In another aspect, the invention concerns an isolated PRO1104 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 through about 341, inclusive of Figure 214 (SEQ ID NO:297).

In a further aspect, the invention concerns an isolated PRO1104 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 23 through 341 of Figure 214 (SEQ ID NO:297).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1104 polypeptide having the sequence of amino acid residues from about 1 or about 23 to about 341, inclusive of Figure 214 (SEQ ID NO:297), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii)

recovering the polypeptide from the cell culture.

**93. PRO1100**

A cDNA clone (DNA59619-1464) has been identified that encodes a novel polypeptide having multiple transmembrane domains, designated in the present application as "PRO1100."

5 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1100 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1100 polypeptide having  
10 the sequence of amino acid residues from about 1 or 21 to about 320, inclusive of Figure 216 (SEQ ID NO:299), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-320, or in another embodiment, 21-320.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1100  
15 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 33 or 93 and about 992, inclusive, of Figure 215 (SEQ ID NO:298). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least  
20 about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203041 (DNA59619-1464), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203041 (DNA59619-1464).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 21 to about 320, inclusive of Figure 216 (SEQ ID NO:299), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1100 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 320, inclusive of Figure 216 (SEQ ID NO:299), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an  
35 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1100 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domains deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule.

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 21 to about 320, inclusive of Figure 216 (SEQ ID NO:299), or (b) the complement of the DNA of (a).

10 In another embodiment, the invention provides isolated PRO1100 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1100 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 21 through 320 of Figure 216 (SEQ ID NO:299).

15 In another aspect, the invention concerns an isolated PRO1100 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 21 to about 320, inclusive of Figure 216 (SEQ ID NO:299).

20 In a further aspect, the invention concerns an isolated PRO1100 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 21 through 320 of Figure 216 (SEQ ID NO:299).

25 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1100 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 320, inclusive of Figure 216 (SEQ ID NO:299), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

30 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1100 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1100 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1100 polypeptide, by contacting the native PRO1100 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

35 In a still further embodiment, the invention concerns a composition comprising a PRO1100 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.



94. **PRO836**

A cDNA clone (DNA59620-1463) has been identified, having some sequence identity with SLS1 that encodes a novel polypeptide, designated in the present application as "PRO836."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO836 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO836 polypeptide having the sequence of amino acid residues from about 1 or 30 to about 461, inclusive of Figure 218 (SEQ ID NO:301), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic  
10 acids is meant to refer to two alternative embodiments provided herein, i.e., 1-461, or in another embodiment, 30-461.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO836 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 65 or 152 and about 1447, inclusive, of Figure 217 (SEQ ID NO:300). Preferably, hybridization occurs under  
15 stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209989  
20 (DNA59620-1463), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209989 (DNA59620-1463).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
25 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 30 to about 461, inclusive of Figure 218 (SEQ ID NO:301), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO836 polypeptide  
30 having the sequence of amino acid residues from about 1 or 30 to about 461, inclusive of Figure 218 (SEQ ID NO:301), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the

amino acid sequence of residues 1 or 30 to about 461, inclusive of Figure 218 (SEQ ID NO:301), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO836 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO836 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 30 through 461 of Figure 218 (SEQ ID NO:301).

In another aspect, the invention concerns an isolated PRO836 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 30 to about 461, inclusive of Figure 218 (SEQ ID NO:301).

In a further aspect, the invention concerns an isolated PRO836 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 30 through 461 of Figure 218 (SEQ ID NO:301).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO836 polypeptide having the sequence of amino acid residues from about 1 or 30 to about 461, inclusive of Figure 218 (SEQ ID NO:301), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO836 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO836 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO836 polypeptide, by contacting the native PRO836 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO836 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 95. PRO1141

A cDNA clone (DNA59625-1498) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO1141".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1141 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most

preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1141 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303), or (b) the complement of the DNA molecule of (a).

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1141 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 204 or about 261 and about 944, inclusive, of Figure 219 (SEQ ID NO:302). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209992 (DNA59625-1498) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209992 (DNA59625-1498).

15 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303), or (b) the complement of the DNA of (a).

20 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1141 polypeptide having the sequence of amino acid residues from 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

25 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1141 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 19 in the sequence of Figure 220 (SEQ ID NO:303). The transmembrane domains have been tentatively identified as extending from about amino acid position 38 to about amino acid position 57, from about amino acid position 67 to about amino acid position 83, from about amino acid position 117 to about amino acid position 139 and from about amino acid position 153 to about amino acid position 170, in the PRO1141 amino acid sequence (Figure 220, SEQ ID NO:303).

35 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the



amino acid sequence of residues 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1141 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 219 (SEQ ID NO:302).

In another embodiment, the invention provides isolated PRO1141 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1141 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 20 to about 247 of Figure 220 (SEQ ID NO:303).

In another aspect, the invention concerns an isolated PRO1141 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303).

In a further aspect, the invention concerns an isolated PRO1141 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303).

In yet another aspect, the invention concerns an isolated PRO1141 polypeptide, comprising the sequence of amino acid residues 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303), or a fragment thereof sufficient to provide a binding site for an anti-PRO1141 antibody. Preferably, the PRO1141 fragment retains a qualitative biological activity of a native PRO1141 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1141 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 247, inclusive of Figure 220 (SEQ ID NO:303), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA33128 comprising the nucleotide sequence of SEQ ID NO:304 (see Figure 221).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA34256 comprising the nucleotide sequence of SEQ ID NO:305 (see Figure 222).

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA47941 comprising the nucleotide sequence of SEQ ID NO:306 (see Figure 223).



In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA54389 comprising the nucleotide sequence of SEQ ID NO:307 (see Figure 224).

96. **PRO1132**

5 A cDNA clone (DNA59767-1489) has been identified that encodes a novel polypeptide having sequence identity with serine proteases and trypsinogen and designated in the present application as "PRO1132."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1132 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1132 polypeptide having the sequence of amino acid residues from about 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1132 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 420 and about 1232, inclusive, of Figure 225 (SEQ ID NO:308). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203108 (DNA59767-1489), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203108 (DNA59767-1489).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1132 polypeptide having the sequence of amino acid residues from about 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more

preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1132 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1132 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1132 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 23 through 293 of Figure 226 (SEQ ID NO:309).

In another aspect, the invention concerns an isolated PRO1132 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309).

In a further aspect, the invention concerns an isolated PRO1132 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 through 293 of Figure 226 (SEQ ID NO:309).

In yet another aspect, the invention concerns an isolated PRO1132 polypeptide, comprising the sequence of amino acid residues 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309), or a fragment thereof sufficient to provide a binding site for an anti-PRO1132 antibody. Preferably, the PRO1132 fragment retains a qualitative biological activity of a native PRO1132 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1132 polypeptide having the sequence of amino acid residues from about 23 to about 293, inclusive of Figure 226 (SEQ ID NO:309), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1132 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1132 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1132 polypeptide, by contacting the native PRO1132 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1132 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**97. PRO1346**

5 A cDNA clone (DNA59776-1600) has been identified, that encodes a novel polypeptide, designated in the present application as PRO1346 (or NL7), having homology to known TIE ligands.

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding an NL7 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding an NL7 polypeptide having the sequence of amino acid residues from about 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding an NL7 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 1-3 (ATG) and about 1381-1383 (CGC, preceding the TAG stop codon), inclusive, of Figure 227 (SEQ ID NO:313). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203128 (DNA59776-1600), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203128 (DNA59776-1600).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 1000 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding an NL7 polypeptide having the sequence of amino acid residues from about 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding an NL7 polypeptide, with or without the initiating methionine, or its soluble forms, i.e. transmembrane domain

deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domain has been tentatively identified as extending from about amino acid position 31 to about amino acid position 50 in the NL7 amino acid sequence (Figure 228, SEQ ID NO:314).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule, at least about 200 bases in length, which encodes a fragment of a native NL7 polypeptide.

In another embodiment, the invention provides an isolated NL7 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides an isolated native sequence NL7 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues from about 51 to about 461 of Figure 228 (SEQ ID NO:314).

In another aspect, the invention concerns an isolated NL7 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314).

In a further aspect, the invention concerns an isolated NL7 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 51 to 461 of Figure 228 (SEQ ID NO:314).

In yet another aspect, the invention concerns an isolated NL7 polypeptide, comprising the sequence of amino acid residues from about 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314), or a fragment thereof sufficient to provide a binding site for an anti-NL7 antibody. Preferably, the NL7 fragment retains a qualitative biological activity of a native NL7 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding an NL7 polypeptide having the sequence of amino acid residues from about 51 to about 461, inclusive of Figure 228 (SEQ ID NO:314), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native NL7 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-NL7 antibody.



In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native NL7 polypeptide, by contacting the native NL7 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising an NL7 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

5  
98. **PRO1131**

A cDNA clone (DNA59777-1480) has been identified that encodes a novel polypeptide having sequence identity with LDL receptors and designated in the present application as "PRO1131."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1131 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1131 polypeptide having the sequence of amino acid residues from about 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1131 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 144 and about 983, inclusive, of Figure 229 (SEQ ID NO:318). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203111 (DNA59777-1480), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
25 Deposit No. 203111 (DNA59777-1480).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1131 polypeptide having the sequence of  
35 amino acid residues from about 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most

preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1131 polypeptide in its soluble form, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domain (type II) has been tentatively identified as extending from about amino acid positions 49-74 in the amino acid sequence of Figure 230, SEQ ID NO:319.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1131 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1131 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1131 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 280 of Figure 230 (SEQ ID NO:319).

In another aspect, the invention concerns an isolated PRO1131 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319).

In a further aspect, the invention concerns an isolated PRO1131 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 280 of Figure 230 (SEQ ID NO:319).

In yet another aspect, the invention concerns an isolated PRO1131 polypeptide, comprising the sequence of amino acid residues 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319), or a fragment thereof sufficient to provide a binding site for an anti-PRO1131 antibody. Preferably, the PRO1131 fragment retains a qualitative biological activity of a native PRO1131 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1131 polypeptide having the sequence of amino acid residues from about 1 to about 280, inclusive of Figure 230 (SEQ ID NO:319), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising

the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1131 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1131 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1131 polypeptide, by contacting the native PRO1131 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1131 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

10 In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA43546 comprising the nucleotide sequence of Figure 231 (SEQ ID NO:320).

#### 99. PRO1281

A cDNA clone (DNA59820-1549) has been identified that encodes a novel secreted polypeptide designated in the present application as "PRO1281".

15 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1281 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1281 polypeptide having  
20 the sequence of amino acid residues from about 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1281 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 273 and about 2552, inclusive, of Figure 232 (SEQ ID NO:325). Preferably, hybridization occurs under stringent  
25 hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203129  
30 (DNA59820-1549), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203129 (DNA59820-1549).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
35 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326), or the complement of the DNA of (a).



In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1281 polypeptide having the sequence of amino acid residues from about 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1281 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 15 in the sequence of Figure 233 (SEQ ID NO:326).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1281 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1281 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1281 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 16 to 775 of Figure 233 (SEQ ID NO:326).

In another aspect, the invention concerns an isolated PRO1281 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326).

In a further aspect, the invention concerns an isolated PRO1281 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 16 to 775 of Figure 233 (SEQ ID NO:326).

In yet another aspect, the invention concerns an isolated PRO1281 polypeptide, comprising the sequence of amino acid residues 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326), or a fragment thereof sufficient to provide a binding site for an anti-PRO1281 antibody. Preferably, the PRO1281 fragment retains a qualitative biological activity of a native PRO1281 polypeptide.



In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1281 polypeptide having the sequence of amino acid residues from about 16 to about 775, inclusive of Figure 233 (SEQ ID NO:326), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

**100. PRO1064**

10 A cDNA clone (DNA59827-1426) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO1064".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1064 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1064 polypeptide having the sequence of amino acid residues from about 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1064 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 532 or about 604 and about 990, inclusive, of Figure 234 (SEQ ID NO:333). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203089 (DNA59827-1426) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203089 (DNA59827-1426).

30 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334), or (b) the complement of the DNA of (a).

35 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1064 polypeptide having the sequence of amino acid residues from 1 or about 25 to

about 153, inclusive of Figure 235 (SEQ ID NO:334), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1064 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 24 in the sequence of Figure 235 (SEQ ID NO:334). The transmembrane domain has been tentatively identified as extending from about amino acid position 89 to about amino acid position 110 in the PRO1064 amino acid sequence (Figure 235, SEQ ID NO:334).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334), or (b) 15 the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1064 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived 20 from the nucleotide sequence shown in Figure 234 (SEQ ID NO:333).

In another embodiment, the invention provides isolated PRO1064 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

25 In a specific aspect, the invention provides isolated native sequence PRO1064 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 25 to about 153 of Figure 235 (SEQ ID NO:334).

In another aspect, the invention concerns an isolated PRO1064 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334).

30 In a further aspect, the invention concerns an isolated PRO1064 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334).

35 In yet another aspect, the invention concerns an isolated PRO1064 polypeptide, comprising the sequence of amino acid residues 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334), or a fragment thereof sufficient to provide a binding site for an anti-PRO1064 antibody. Preferably, the PRO1064 fragment retains a qualitative biological activity of a native PRO1064 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1064 polypeptide having the sequence of amino acid residues from about 1 or about 25 to about 153, inclusive of Figure 235 (SEQ ID NO:334), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In another embodiment, the invention provides an expressed sequence tag (EST) designated herein as DNA45288 comprising the nucleotide sequence of SEQ ID NO:335 (see Figure 236).

#### 101. PRO1379

A cDNA clone (DNA59828-1608) has been identified that encodes a novel secreted polypeptide designated in the present application as "PRO1379."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1379 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1379 polypeptide having the sequence of amino acid residues from about 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1379 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 61 and about 1731, inclusive, of Figure 237 (SEQ ID NO:339). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203158 (DNA59828-1608), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203158 (DNA59828-1608).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340), or the complement of the DNA of (a).



In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1379 polypeptide having the sequence of amino acid residues from about 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1379 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 17 in the sequence of Figure 238 (SEQ ID NO:340).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1379 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1379 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1379 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 18 to 574 of Figure 238 (SEQ ID NO:340).

In another aspect, the invention concerns an isolated PRO1379 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340).

In a further aspect, the invention concerns an isolated PRO1379 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 18 to 574 of Figure 238 (SEQ ID NO:340).

In yet another aspect, the invention concerns an isolated PRO1379 polypeptide, comprising the sequence of amino acid residues 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340), or a fragment thereof sufficient to provide a binding site for an anti-PRO1379 antibody. Preferably, the PRO1379 fragment retains a qualitative biological activity of a native PRO1379 polypeptide.



In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1379 polypeptide having the sequence of amino acid residues from about 18 to about 574, inclusive of Figure 238 (SEQ ID NO:340), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

102. PRO844

10 A cDNA clone (DNA59838-1462) has been identified, having sequence identity with protease inhibitors, that encodes a novel polypeptide, designated in the present application as "PRO844."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO844 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO844 polypeptide having the sequence of amino acid residues from about 1 or 20 to about 111, inclusive of Figure 240 (SEQ ID NO:345), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-111, or in another embodiment, 20 20-111.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO844 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 5 or 62 and about 337, inclusive, of Figure 239 (SEQ ID NO:344). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209976 (DNA59838-1462), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC 30 Deposit No. 209976 (DNA59838-1462).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 20 to about 111, inclusive of Figure 240 (SEQ ID NO:345), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO844 polypeptide having the sequence of amino acid residues from about 1 or 20 to about 111, inclusive of Figure 240 (SEQ ID NO:345), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 20 to about 111, inclusive of Figure 240 (SEQ ID NO:345), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO844 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO844 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 20 through 111 of Figure 240 (SEQ ID NO:345).

In another aspect, the invention concerns an isolated PRO844 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 20 to about 111, inclusive of Figure 240 (SEQ ID NO:345).

In a further aspect, the invention concerns an isolated PRO844 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 20 through 111 of Figure 240 (SEQ ID NO:345).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO844 polypeptide having the sequence of amino acid residues from about 1 or 20 to about 111, inclusive of Figure 240 (SEQ ID NO:345), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO844 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO844 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO844 polypeptide, by contacting the native PRO844 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO844 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**103. PRO848**

5 A cDNA clone (DNA59839-1461) has been identified, having sequence identity with sialyltransferases that encodes a novel polypeptide, designated in the present application as "PRO848."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO848 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO848 polypeptide having the sequence of amino acid residues from about 1 or 36 to about 600, inclusive of Figure 242 (SEQ ID NO:347), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-600, or in another embodiment, 36-600.

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO848 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 1 or 251 and about 1945, inclusive, of Figure 241 (SEQ ID NO:346). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209988 (DNA59839-1461), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
25 Deposit No. 209988 (DNA59839-1461).

30 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 36 to about 600, inclusive of Figure 242 (SEQ ID NO:347), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO848 polypeptide having the sequence of amino acid residues from about 1 or 36 to about 600, inclusive of Figure 242 (SEQ ID NO:347), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an  
35 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.



In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 36 to about 600, inclusive of Figure 242 (SEQ ID NO:347), or (b) the complement of the DNA of (a).

5 In another embodiment, the invention provides isolated PRO848 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO848 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 36 through 600 of Figure 242 (SEQ ID NO:347).

10 In another aspect, the invention concerns an isolated PRO848 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 36 to about 600, inclusive of Figure 242 (SEQ ID NO:347).

15 In a further aspect, the invention concerns an isolated PRO848 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 36 through 600 of Figure 242 (SEQ ID NO:347).

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO848 polypeptide having the sequence of amino acid residues from about 1 or 36 to about 600, inclusive of Figure 242 (SEQ ID NO:347), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii)  
25 recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO848 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO848 antibody.

30 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO848 polypeptide, by contacting the native PRO848 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO848 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 104. PRO1097

35 Applicants have identified a cDNA clone (DNA59841-1460) that encodes a novel secreted polypeptide having domains therein from the glycoprotease family proteins and the acyltransferase ChoActase/COT/CPT family, wherein the polypeptide is designated in the present application as "PRO1097".



In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1097 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1097 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 91, inclusive of Figure 244 (SEQ ID NO:349), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-91, or in another embodiment, 21-91.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1097 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 3 or 63 and about 275, inclusive, of Figure 243 (SEQ ID NO:348). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203044 (DNA59841-1460), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203044 (DNA59841-1460).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 21 to about 91, inclusive of Figure 244 (SEQ ID NO:349), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1097 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 91, inclusive of Figure 244 (SEQ ID NO:349), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1097 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 20 in the sequence of Figure 244 (SEQ ID NO:349).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more

preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 21 to about 91, inclusive of Figure 244 (SEQ ID NO:349), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1097 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

5 In a specific aspect, the invention provides isolated native sequence PRO1097 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 21 through 91 of Figure 244 (SEQ ID NO:349).

10 In another aspect, the invention concerns an isolated PRO1097 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 21 to about 91, inclusive of Figure 244 (SEQ ID NO:349).

15 In a further aspect, the invention concerns an isolated PRO1097 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 21 through 91 of Figure 244 (SEQ ID NO:349).

20 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1097 polypeptide having the sequence of amino acid residues from about 1 or 21 to about 91, inclusive of Figure 244 (SEQ ID NO:349), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

25 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1097 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1097 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1097 polypeptide, by contacting the native PRO1097 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

30 In a still further embodiment, the invention concerns a composition comprising a PRO1097 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 105. PRO1153

A cDNA clone (DNA59842-1502) has been identified, having two transmembrane domains and being very proline rich, that encodes a novel polypeptide, designated in the present application as "PRO1153."

35 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1153 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1153 polypeptide having the sequence of amino acid residues from about 1 to about 197, inclusive of Figure 246 (SEQ ID NO:351), or (b) the complement of the DNA molecule of (a).

5 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1153 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 92 and about 682, inclusive, of Figure 245 (SEQ ID NO:350). Preferably, hybridization occurs under stringent hybridization and wash conditions.

10 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209982 (DNA59842-1502), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
15 Deposit No. 209982 (DNA59842-1502).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 197, inclusive of Figure 246 (SEQ ID  
20 NO:351), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1153 polypeptide having the sequence of amino acid residues from about 1 to about 197, inclusive of Figure 246 (SEQ ID NO:351), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an  
25 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1153 polypeptide, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is  
30 complementary to such encoding nucleic acid molecule. The transmembrane domains have been tentatively identified as extending from about amino acid positions 10-28 and 85-110 in the PRO1153 amino acid sequence (Figure 246, SEQ ID NO:351).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more  
35 preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 197, inclusive of Figure 246 (SEQ ID NO:351), or (b) the complement of the DNA of (a).



In another embodiment, the invention provides isolated PRO1153 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1153 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 197 of Figure 246 (SEQ ID NO:351).

5 In another aspect, the invention concerns an isolated PRO1153 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 197, inclusive of Figure 246 (SEQ ID NO:351).

10 In a further aspect, the invention concerns an isolated PRO1153 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 197 of Figure 246 (SEQ ID NO:351).

15 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1153 polypeptide having the sequence of amino acid residues from about 1 to about 197, inclusive of Figure 246 (SEQ ID NO:351), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

20

**106. PRO1154**

A cDNA clone (DNA59846-1503) has been identified that encodes a novel aminopeptidase, designated in the present application as "PRO1154."

25 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1154 polypeptide.

30 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1154 polypeptide having the sequence of amino acid residues from about 1 or 35 to about 941, inclusive of Figure 248 (SEQ ID NO:353), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1154 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 86 or 188 and about 2908, inclusive, of Figure 247 (SEQ ID NO:352). Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule



encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209978 (DNA59846-1503), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209978 (DNA59846-1503).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 35 to about 941, inclusive of Figure 248 (SEQ ID NO:353), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1154 polypeptide having the sequence of amino acid residues from about 1 or 35 to about 941, inclusive of Figure 258 (SEQ ID NO:353), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA  
15 molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 35 to about 941, inclusive of Figure 248 (SEQ ID NO:353), or (b) the  
20 complement of the DNA of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule consisting essentially of DNA encoding a polypeptide having amino acids 1 or 35 through about 73 of SEQ ID NO:353.

In another embodiment, the invention provides isolated PRO1154 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

25 In a specific aspect, the invention provides isolated native sequence PRO1154 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 35 to 941 of Figure 248 (SEQ ID NO:353).

In a specific aspect, the invention provides a polypeptide having amino acids 1 or 35 through about 73 of SEQ ID NO:353.

30 In another aspect, the invention concerns an isolated PRO1154 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 35 to about 941, inclusive of Figure 248 (SEQ ID NO:353).

In a further aspect, the invention concerns an isolated PRO1154 polypeptide, comprising an amino acid  
35 sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 35 through 941 of Figure 248 (SEQ ID NO:353).

In yet another aspect, the invention concerns an isolated PRO1154 polypeptide, comprising the sequence of amino acid residues 1 or 35 to about 941, inclusive of Figure 248 (SEQ ID NO:353), or a fragment thereof sufficient to provide a binding site for an anti-PRO1154 antibody. Preferably, the PRO1154 fragment retains a qualitative biological activity of a native PRO1154 polypeptide.

5 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1154 polypeptide having the sequence of amino acid residues from about 1 or 35 to about 941, inclusive of Figure 248 (SEQ ID NO:353), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell  
10 comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1154 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1154 antibody.

15 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1154 polypeptide, by contacting the native PRO1154 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1154 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

20 **107. PRO1181**

A cDNA clone (DNA59847-1511) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1181".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1181 polypeptide.

25 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1181 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355), or (b) the complement of the DNA molecule of (a).

30 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1181 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 17 or about 62 and about 1327, inclusive, of Figure 249 (SEQ ID NO:354). Preferably, hybridization occurs under stringent hybridization and wash conditions.

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203098

(DNA59847-1511) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203098 (DNA59847-1511).

5 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355), or (b) the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1181 polypeptide having the sequence of amino acid residues from 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

15 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1181 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 15 in the sequence of Figure 250 (SEQ ID NO:355). The transmembrane domain is at amino acids positions 243-260 of Figure 250.

20 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355), or (b) the complement of the DNA of (a).

25 Another embodiment is directed to fragments of a PRO1181 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 249 (SEQ ID NO:354).

30 In another embodiment, the invention provides isolated PRO1181 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1181 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 16 to about 437 of Figure 250 (SEQ ID NO:355).

35 In another aspect, the invention concerns an isolated PRO1181 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the



sequence of amino acid residues 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355).

In a further aspect, the invention concerns an isolated PRO1181 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355).

5 In yet another aspect, the invention concerns an isolated PRO1181 polypeptide, comprising the sequence of amino acid residues 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355), or a fragment thereof sufficient to provide a binding site for an anti-PRO1181 antibody. Preferably, the PRO1181 fragment retains a qualitative biological activity of a native PRO1181 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1181 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 437, inclusive of Figure 250 (SEQ ID NO:355), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host  
15 cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

#### 108. PRO1182

A cDNA clone (DNA59848-1512) has been identified, having homology to nucleic acid encoding  
20 conglutinin that encodes a novel polypeptide, designated in the present application as "PRO1182".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1182 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most  
25 preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1182 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1182 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 67  
30 or about 142 and about 879, inclusive, of Figure 251 (SEQ ID NO:356). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule  
35 encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203088 (DNA59848-1512) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in



ATCC Deposit No. 203088 (DNA59848-1512).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1182 polypeptide having the sequence of amino acid residues from 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1182 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 25 in the sequence of Figure 252 (SEQ ID NO:357).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1182 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 251 (SEQ ID NO:356).

In another embodiment, the invention provides isolated PRO1182 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1182 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 26 to about 271 of Figure 252 (SEQ ID NO:357).

In another aspect, the invention concerns an isolated PRO1182 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357).

In a further aspect, the invention concerns an isolated PRO1182 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357).

5 In yet another aspect, the invention concerns an isolated PRO1182 polypeptide, comprising the sequence of amino acid residues 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357), or a fragment thereof sufficient to provide a binding site for an anti-PRO1182 antibody. Preferably, the PRO1182 fragment retains a qualitative biological activity of a native PRO1182 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1182 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 271, inclusive of Figure 252 (SEQ ID NO:357), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii)  
15 recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1182 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1182 antibody.

20 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1182 polypeptide by contacting the native PRO1182 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1182 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 109. PRO1155

25 A cDNA clone (DNA59849-1504) has been identified, having sequence identity with neurokinin B that encodes a novel polypeptide, designated in the present application as "PRO1155."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1155 polypeptide.

30 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1155 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 135, inclusive of Figure 254 (SEQ ID NO:359), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to nucleic or amino acids is meant to convey alternative embodiments, i.e., 1-135 or alternatively in another embodiment, 19-135.

35 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1155 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 158 or 212 and about 562, inclusive, of Figure 253 (SEQ ID NO:358). Preferably, hybridization occurs under stringent

hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209986 (DNA59849-1504), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209986 (DNA59849-1504).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 19 to about 135, inclusive of Figure 254 (SEQ ID NO:359), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1155 polypeptide having the sequence of amino acid residues from about 19 to about 135, inclusive of Figure 254 (SEQ ID NO:359), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 19 to about 135, inclusive of Figure 254 (SEQ ID NO:359), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1155 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1155 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 19 through 135 of Figure 254 (SEQ ID NO:359).

In another aspect, the invention concerns an isolated PRO1155 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 19 to about 135, inclusive of Figure 254 (SEQ ID NO:359).

In a further aspect, the invention concerns an isolated PRO1155 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 19 through 135 of Figure 254 (SEQ ID NO:359).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1155 polypeptide having the sequence of amino acid residues from about 1 or 19 to about 135, inclusive of Figure 254 (SEQ ID NO:359), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1155 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1155 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1155 polypeptide, by contacting the native PRO1155 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1155 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 110. PRO1156

A cDNA clone (DNA59853-1505) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1156."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1156 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1156 polypeptide having the sequence of amino acid residues from about 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1156 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 281 and about 688, inclusive, of Figure 255 (SEQ ID NO:360). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209985 (DNA59853-1505), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209985 (DNA59853-1505).



In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361), or the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 50 nucleotides, preferably at least 100 nucleotides, and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1156 polypeptide having the sequence of amino acid residues from about 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably  
10 at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1156 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is  
15 complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 to about amino acid position 22 in the sequence of Figure 256 (SEQ ID NO:361).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
20 amino acid sequence of residues 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361), or (b) the complement of the DNA of (a).

In another aspect, the invention concerns hybridization probes that comprise fragments of the PRO784 coding sequence, or complementary sequence thereof. The hybridization probes preferably have at least about 20 nucleotides to about 80 nucleotides, and more preferably, at least about 20 to about 50 nucleotides.

25 In another embodiment, the invention provides isolated PRO1156 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1156 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 23 to 159 of Figure 256 (SEQ ID NO:361).

In another aspect, the invention concerns an isolated PRO1156 polypeptide, comprising an amino acid  
30 sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361).

In a further aspect, the invention concerns an isolated PRO1156 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least  
35 about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 to 159 of Figure 256 (SEQ ID NO:361).

In yet another aspect, the invention concerns an isolated PRO1156 polypeptide, comprising the sequence of amino acid residues 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361), or a fragment thereof sufficient to provide a binding site for an anti-PRO1156 antibody. Preferably, the PRO1156 fragment retains a qualitative biological activity of a native PRO1156 polypeptide.

5 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1156 polypeptide having the sequence of amino acid residues from about 23 to about 159, inclusive of Figure 256 (SEQ ID NO:361), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising  
10 the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

#### 111. PRO1098

15 A cDNA clone (DNA59854-1459) has been identified which encodes a novel polypeptide, designated in the present application as "PRO1098."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1098 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most  
20 preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1098 polypeptide having the sequence of amino acid residues from about 1 or 20 to about 78, inclusive of Figure 258 (SEQ ID NO:363), or (b) the complement of the DNA molecule of (a). The term "or" as used herein to refer to amino or nucleic acids is meant to refer to two alternative embodiments provided herein, i.e., 1-78, or in another embodiment, 20-78.

25 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1098 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 58 or 115 and about 291, inclusive, of Figure 257 (SEQ ID NO:362). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
30 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209974 (DNA59854-1459), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
35 Deposit No. 209974 (DNA59854-1459).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence

identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 20 to about 78, inclusive of Figure 258 (SEQ ID NO:363), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1098 polypeptide having the sequence of amino acid residues from about 1 or 20 to about 78, inclusive of Figure 258 (SEQ ID NO:363), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 20 to about 78, inclusive of Figure 258 (SEQ ID NO:363), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1098 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1098 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 20 through 78 of Figure 258 (SEQ ID NO:363).

In another aspect, the invention concerns an isolated PRO1098 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 20 to about 78, inclusive of Figure 258 (SEQ ID NO:363).

In a further aspect, the invention concerns an isolated PRO1098 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 20 through 78 of Figure 258 (SEQ ID NO:363).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1098 polypeptide having the sequence of amino acid residues from about 1 or 20 to about 78, inclusive of Figure 258 (SEQ ID NO:363), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

**112. PRO1127**

A cDNA clone (DNA60283-1484) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1127."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1127 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1127 polypeptide having the sequence of amino acid residues from about 1 or 30 to about 67, inclusive of Figure 260 (SEQ ID NO:365), or (b) the complement of the DNA molecule of (a). The term "or" in reference to amino or nucleic acids as used  
10 herein refers to two alternative embodiments, i.e., 1-67 in one embodiment, or alternatively, 30-67.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1127 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 126 or 213 and about 326, inclusive, of Figure 259 (SEQ ID NO:364). Preferably, hybridization occurs under stringent hybridization and wash conditions.

15 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203043 (DNA60283-1484), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic  
20 acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203043 (DNA60283-1484).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
25 identity to the sequence of amino acid residues from about 1 or 30 to about 67, inclusive of Figure 260 (SEQ ID NO:365), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1127 polypeptide having the sequence of amino acid residues from about 1 or 30 to about 67, inclusive of Figure 260 (SEQ ID  
30 NO:365), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding  
35 a PRO1127 polypeptide without the N-terminal signal sequence and/or the initiating methionine. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 29 in the sequence of Figure 260 (SEQ ID NO:365).



In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 30 to about 67, inclusive of Figure 260 (SEQ ID NO:365), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1127 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 through about 80 nucleotides in length, preferably from about 20 through about 60 nucleotides in length, more preferably from about 20 through about 50 nucleotides in length, and most preferably from about 20 through about 40 nucleotides in length.

10 In another embodiment, the invention provides isolated PRO1127 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1127 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 30 through 67 of Figure 260 (SEQ ID NO:365).

15 In another aspect, the invention concerns an isolated PRO1127 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 30 to about 67, inclusive of Figure 260 (SEQ ID NO:365).

20 In a further aspect, the invention concerns an isolated PRO1127 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 30 through 67 of Figure 260 (SEQ ID NO:365).

25 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1127 polypeptide having the sequence of amino acid residues from about 1 or 30 to about 67, inclusive of Figure 260 (SEQ ID NO:365), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

30 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1127 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1127 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1127 polypeptide, by contacting the native PRO1127 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

35 In a still further embodiment, the invention concerns a composition comprising a PRO1127 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**113. PRO1126**

A cDNA clone (DNA60615-1483) has been identified, having homology to nucleic acid encoding olfactomedin that encodes a novel polypeptide, designated in the present application as "PRO1126".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1126 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1126 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1126 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 110 or about 185 and about 1315, inclusive, of Figure 261 (SEQ ID NO:366). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209980 (DNA60615-1483) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
20 ATCC Deposit No. 209980 (DNA60615-1483).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID  
25 NO:367), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1126 polypeptide having the sequence of amino acid residues from 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367), or (b) the complement of the DNA molecule of (a), and,  
30 if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95 % sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1126 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is  
35 complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 25 in the sequence of Figure 262 (SEQ ID NO:367).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1126 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 261 (SEQ ID NO:366).

10 In another embodiment, the invention provides isolated PRO1126 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1126 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 26 to about 402 of Figure 262 (SEQ ID NO:367).

15 In another aspect, the invention concerns an isolated PRO1126 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367).

20 In a further aspect, the invention concerns an isolated PRO1126 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367).

25 In yet another aspect, the invention concerns an isolated PRO1126 polypeptide, comprising the sequence of amino acid residues 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367), or a fragment thereof sufficient to provide a binding site for an anti-PRO1126 antibody. Preferably, the PRO1126 fragment retains a qualitative biological activity of a native PRO1126 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1126 polypeptide having the sequence of amino acid residues from about 1 or about 26 to about 402, inclusive of Figure 262 (SEQ ID NO:367), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1126 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1126 antibody.



In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1126 polypeptide by contacting the native PRO1126 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1126 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

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#### 114. PRO1125

A cDNA clone (DNA60619-1482) has been identified, having beta-transducin family Trp-Asp (WD) conserved regions, that encodes a novel polypeptide, designated in the present application as "PRO1125."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1125 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1125 polypeptide having the sequence of amino acid residues from about 1 or 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369),  
15 or (b) the complement of the DNA molecule of (a). As used herein, "or" when referring to nucleic acids or amino acids, refers to two alternative embodiments, i.e., 1-447 and 26-447.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1125 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 47 or 122 and about 1387, inclusive, of Figure 263 (SEQ ID NO:368). Preferably, hybridization occurs under  
20 stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209993  
25 (DNA60619-1482), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209993 (DNA60619-1482).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
30 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1125 polypeptide  
35 having the sequence of amino acid residues from about 1 or 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90 %



sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1125 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 25 in the sequence of Figure 264 (SEQ ID NO:369).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369), or (b) the complement of the DNA of (a).

In another embodiment, the invention provides isolated PRO1125 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1125 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 26 to 447 of Figure 264 (SEQ ID NO:369).

In another aspect, the invention concerns an isolated PRO1125 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369).

In a further aspect, the invention concerns an isolated PRO1125 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 26 through 447 of Figure 264 (SEQ ID NO:369).

In yet another aspect, the invention concerns an isolated PRO1125 polypeptide, comprising the sequence of amino acid residues 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369), or a fragment thereof sufficient to provide a binding site for an anti-PRO1125 antibody. Preferably, the PRO1125 fragment retains a qualitative biological activity of a native PRO1125 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1125 polypeptide having the sequence of amino acid residues from about 26 to about 447, inclusive of Figure 264 (SEQ ID NO:369), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1125 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1125 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1125 polypeptide, by contacting the native PRO1125 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

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115. **PRO1186**

A cDNA clone (DNA60621-1516) has been identified that encodes a novel polypeptide having sequence identity with venom protein A and designated in the present application as "PRO1186."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1186 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1186 polypeptide having the sequence of amino acid residues from about 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1186 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 148 and about 405, inclusive, of Figure 265 (SEQ ID NO:370). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203091 (DNA60621-1516), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic  
25 acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203091 (DNA60621-1516).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1186 polypeptide having the sequence of  
35 amino acid residues from about 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most

preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1186 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 through about 80 nucleotides in length, preferably from about 20 through about 60 nucleotides in length, more preferably from about 20 through about 50 nucleotides in length, and most preferably from about 20 through about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1186 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1186 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 20 through 105 of Figure 266 (SEQ ID NO:371).

In another aspect, the invention concerns an isolated PRO1186 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371).

In a further aspect, the invention concerns an isolated PRO1186 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 20 through 105 of Figure 266 (SEQ ID NO:371).

In yet another aspect, the invention concerns an isolated PRO1186 polypeptide, comprising the sequence of amino acid residues 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371), or a fragment thereof sufficient to provide a binding site for an anti-PRO1186 antibody. Preferably, the PRO1186 fragment retains a qualitative biological activity of a native PRO1186 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1186 polypeptide having the sequence of amino acid residues from about 20 to about 105, inclusive of Figure 266 (SEQ ID NO:371), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1186 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1186 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1186 polypeptide, by contacting the native PRO1186 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1186 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

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**116. PRO1198**

A cDNA clone (DNA60622-1525) has been identified that encodes a novel secreted polypeptide designated in the present application as "PRO1198."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1198 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1198 polypeptide having the sequence of amino acid residues from about 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1198 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 156 and about 740, inclusive, of Figure 268 (SEQ ID NO:373). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203090 (DNA60622-1525), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic  
25 acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203090 (DNA60622-1525).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1198 polypeptide having the sequence of  
35 amino acid residues from about 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most



preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1198 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 through about amino acid position 35 in the sequence of Figure 268 (SEQ ID NO:373).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1198 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1198 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1198 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 35 to 229 of Figure 268 (SEQ ID NO:373).

In another aspect, the invention concerns an isolated PRO1198 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373).

In a further aspect, the invention concerns an isolated PRO1198 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 35 to 229 of Figure 268 (SEQ ID NO:373).

In yet another aspect, the invention concerns an isolated PRO1198 polypeptide, comprising the sequence of amino acid residues 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373), or a fragment thereof sufficient to provide a binding site for an anti-PRO1198 antibody. Preferably, the PRO1198 fragment retains a qualitative biological activity of a native PRO1198 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1198 polypeptide having the sequence of amino acid residues from about 35 to about 229, inclusive of Figure 268 (SEQ ID NO:373), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the

polypeptide from the cell culture.

**117. PRO1158**

A cDNA clone (DNA60625-1507) has been identified that encodes a novel transmembrane polypeptide, designated in the present application as "PRO1158".

5 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1158 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1158 polypeptide having  
10 the sequence of amino acid residues from about 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1158 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 220 and about 531, inclusive, of Figure 269 (SEQ ID NO:374). Preferably, hybridization occurs under stringent  
15 hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209975  
20 (DNA60625-1507), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209975 (DNA60625-1507).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence  
25 identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule  
30 under stringent conditions with (a) a DNA molecule encoding a PRO1158 polypeptide having the sequence of amino acid residues from about 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90 % sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1158 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding

nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 19 in the sequence of Figure 270 (SEQ ID NO:375). The transmembrane domain has been tentatively identified as extending from about amino acid position 56 to about amino acid position 80 in the PRO1158 amino acid sequence (Figure 270, SEQ ID NO:375).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375), or (b) the complement of the DNA of (a).

10 In another aspect, the invention concerns hybridization probes that comprise fragments of the PRO1158 coding sequence, or complementary sequence thereof. The hybridization probes preferably have at least about 20 nucleotides to about 80 nucleotides, and more preferably, at least about 20 to about 50 nucleotides.

In another embodiment, the invention provides isolated PRO1158 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

15 In a specific aspect, the invention provides isolated native sequence PRO1158 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 20 to 123 of Figure 270 (SEQ ID NO:375).

In another aspect, the invention concerns an isolated PRO1158 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375).

20 In a further aspect, the invention concerns an isolated PRO1158 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 20 to 123 of Figure 270 (SEQ ID NO:375).

25 In yet another aspect, the invention concerns an isolated PRO1158 polypeptide, comprising the sequence of amino acid residues 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375), or a fragment thereof sufficient to provide a binding site for an anti-PRO1158 antibody. Preferably, the PRO1158 fragment retains a qualitative biological activity of a native PRO1158 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1158 polypeptide having the sequence of amino acid residues from about 20 to about 123, inclusive of Figure 270 (SEQ ID NO:375), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the  
35 polypeptide from the cell culture.

**118. PRO1159**

A cDNA clone (DNA60627-1508) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1159".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1159 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1159 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1159 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 92 or about 137 and about 361, inclusive, of Figure 271 (SEQ ID NO:376). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203092 (DNA60627-1508) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
20 ATCC Deposit No. 203092 (DNA60627-1508).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID  
25 NO:377), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 10 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1159 polypeptide having the sequence of amino acid residues from 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377), or (b) the complement of the DNA molecule of (a), and,  
30 if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1159 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is  
35 complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 15 in the sequence of Figure 272 (SEQ ID NO:377).



In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1159 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 271 (SEQ ID NO:376).

10 In another embodiment, the invention provides isolated PRO1159 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1159 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 16 to about 90 of Figure 272 (SEQ ID NO:377).

15 In another aspect, the invention concerns an isolated PRO1159 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377).

20 In a further aspect, the invention concerns an isolated PRO1159 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377).

25 In yet another aspect, the invention concerns an isolated PRO1159 polypeptide, comprising the sequence of amino acid residues 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377), or a fragment thereof sufficient to provide a binding site for an anti-PRO1159 antibody. Preferably, the PRO1159 fragment retains a qualitative biological activity of a native PRO1159 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1159 polypeptide having the sequence of amino acid residues from about 1 or about 16 to about 90, inclusive of Figure 272 (SEQ ID NO:377), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

**119. PRO1124**

A cDNA clone (DNA60629-1481) has been identified, having sequence identity with a chloride channel protein and lung-endothelial cell adhesion molecule-1 (EAM-1) that encodes a novel polypeptide, designated in the present application as "PRO1124."

5 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1124 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1124 polypeptide having the sequence of amino acid residues from about 1 or 22 to about 919, inclusive of Figure 274 (SEQ ID NO:379),  
10 or (b) the complement of the DNA molecule of (a). As used herein, "or", i.e., 1 or 22 and 25 or 88, is used to describe two alternative embodiments. For example, the invention includes amino acids 1 through 919 and in an alternative embodiment, provides amino acids 22 through 919, etc.

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1124 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 25 or  
15 88 and about 2781, inclusive, of Figure 273 (SEQ ID NO:378). In another aspect, the invention concerns an isolated nucleic acid molecule hybridizing to the complement of the nucleic acid of SEQ ID NO:378. Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least  
20 about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209979 (DNA60629-1481), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 209979 (DNA60629-1481).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 or 22 to about 919, inclusive of Figure 274 (SEQ ID NO:379), or the complement of the DNA of (a).

30 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1124 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The cytoplasmic end can be excluded as well. The signal peptide has been tentatively identified as extending from amino acid position 1 to about amino acid position 21 in the sequence of Figure 274  
35 (SEQ ID NO: 379). The transmembrane domains have been tentatively identified as extending from about amino acid position 284 to about amino acid position 300 and from about amino acid position 617 to about amino acid position 633 in the amino acid sequence (Figure 274, SEQ ID NO:379).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 22 to about 919, inclusive of Figure 274 (SEQ ID NO:379), or (b) the complement of the DNA of (a).

5 In another embodiment, the invention provides isolated PRO1124 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1124 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 or 22 through 919 of Figure 274 (SEQ ID NO:379).

10 In another aspect, the invention concerns an isolated PRO1124 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or 22 to about 919, inclusive of Figure 274 (SEQ ID NO:379).

In a further aspect, the invention concerns an isolated PRO1124 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or 22 to 919 of Figure 274 (SEQ ID NO:379).

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1124 polypeptide having the sequence of amino acid residues from about 1 or 22 to about 919, inclusive of Figure 274 (SEQ ID NO:379), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1124 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1124 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1124 polypeptide, by contacting the native PRO1124 polypeptide with a candidate molecule and monitoring an activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1124 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

#### 120. PRO1287

35 A cDNA clone (DNA61755-1554) has been identified, having homology to nucleic acid encoding fringe protein, that encodes a novel polypeptide, designated in the present application as "PRO1287".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1287 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1287 polypeptide having the sequence of amino acid residues from about 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1287 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 655 or about 736 and about 2250, inclusive, of Figure 275 (SEQ ID NO:380). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203112 (DNA61755-1554) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203112 (DNA61755-1554).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1287 polypeptide having the sequence of amino acid residues from 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1287 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 27 in the sequence of Figure 276 (SEQ ID NO:381).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the



amino acid sequence of residues 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1287 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 275 (SEQ ID NO:380).

In another embodiment, the invention provides isolated PRO1287 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1287 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 28 to about 532 of Figure 276 (SEQ ID NO:381).

In another aspect, the invention concerns an isolated PRO1287 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381).

In a further aspect, the invention concerns an isolated PRO1287 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381).

In yet another aspect, the invention concerns an isolated PRO1287 polypeptide, comprising the sequence of amino acid residues 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381), or a fragment thereof sufficient to provide a binding site for an anti-PRO1287 antibody. Preferably, the PRO1287 fragment retains a qualitative biological activity of a native PRO1287 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1287 polypeptide having the sequence of amino acid residues from about 1 or about 28 to about 532, inclusive of Figure 276 (SEQ ID NO:381), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1287 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1287 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1287 polypeptide by contacting the native PRO1287 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1287 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**121. PRO1312**

A cDNA clone (DNA61873-1574) has been identified that encodes a novel transmembrane polypeptide designated in the present application as "PRO1312".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1312 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1312 polypeptide having the sequence of amino acid residues from about 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1312 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 49 and about 642, inclusive, of Figure 277 (SEQ ID NO:386). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203132 (DNA61873-1574), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203132 (DNA61873-1574).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1312 polypeptide having the sequence of amino acid residues from about 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1312 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and

its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 14 in the sequence of Figure 278 (SEQ ID NO:387). The transmembrane domain has been tentatively identified as extending from about amino acid position 141 to about amino acid position 160 in the PRO1312 amino acid sequence (Figure 278, SEQ ID NO:387).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO1312 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

15 In another embodiment, the invention provides isolated PRO1312 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1312 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 15 to 212 of Figure 278 (SEQ ID NO:387).

20 In another aspect, the invention concerns an isolated PRO1312 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387).

25 In a further aspect, the invention concerns an isolated PRO1312 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 15 to 212 of Figure 278 (SEQ ID NO:387).

In yet another aspect, the invention concerns an isolated PRO1312 polypeptide, comprising the sequence of amino acid residues 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387), or a fragment thereof sufficient to provide a binding site for an anti-PRO1312 antibody. Preferably, the PRO1312 fragment retains a qualitative biological activity of a native PRO1312 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1312 polypeptide having the sequence of amino acid residues from about 15 to about 212, inclusive of Figure 278 (SEQ ID NO:387), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence  
35 identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.



**122. PRO1192**

A cDNA clone (DNA62814-1521) has been identified that encodes a novel polypeptide having homology to myelin P0 protein and designated in the present application as "PRO1192."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1192 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1192 polypeptide having the sequence of amino acid residues from about 22 to about 215, inclusive of Figure 280 (SEQ ID NO:389), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1192 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 184 and about 764, inclusive, of Figure 279 (SEQ ID NO:388). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203093 (DNA62814-1521), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
20 Deposit No. 203093 (DNA62814-1521).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 22 to about 215, inclusive of Figure 280 (SEQ ID  
25 NO:389), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1192 polypeptide having the sequence of amino acid residues from about 22 to about 215, inclusive of Figure 280 (SEQ ID NO:389), or (b) the  
30 complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1192 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and  
35 its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 21 in the sequence of Figure 280 (SEQ ID NO:389). The transmembrane



domain has been tentatively identified as extending from about amino acid position 153 through about amino acid position 176 in the PRO1192 amino acid sequence (Figure 280, SEQ ID NO:389).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 22 to about 215, inclusive of Figure 280 (SEQ ID NO:389), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1192 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1192 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1192 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 22 to 215 of Figure 280 (SEQ ID NO:389).

In another aspect, the invention concerns an isolated PRO1192 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 22 to about 215, inclusive of Figure 280 (SEQ ID NO:389).

In a further aspect, the invention concerns an isolated PRO1192 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 22 to 215 of Figure 280 (SEQ ID NO:389).

In yet another aspect, the invention concerns an isolated PRO1192 polypeptide, comprising the sequence of amino acid residues 22 to about 215, inclusive of Figure 280 (SEQ ID NO:389), or a fragment thereof sufficient to provide a binding site for an anti-PRO1192 antibody. Preferably, the PRO1192 fragment retains a qualitative biological activity of a native PRO1192 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1192 polypeptide having the sequence of amino acid residues from about 22 to about 215, inclusive of Figure 280 (SEQ ID NO:389), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1192 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1192 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1192 polypeptide, by contacting the native PRO1192 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1192 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

5  
**123. PRO1160**

A cDNA clone (DNA62872-1509) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1160".

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1160 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1160 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID  
15 NO:394), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1160 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 40 or about 97 and about 309, inclusive, of Figure 282 (SEQ ID NO:394). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203100 (DNA62872-1509) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the  
25 nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203100 (DNA62872-1509).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID NO:394), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1160 polypeptide having the sequence of amino acid residues from 1 or about 20 to  
35 about 90, inclusive of Figure 282 (SEQ ID NO:394), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85 % sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence

identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1160 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 19 in the sequence of Figure 282 (SEQ ID NO:394).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID NO:394), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1160 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 281 (SEQ ID NO:393).

In another embodiment, the invention provides isolated PRO1160 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1160 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 20 to about 90 of Figure 282 (SEQ ID NO:394).

In another aspect, the invention concerns an isolated PRO1160 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID NO:394).

In a further aspect, the invention concerns an isolated PRO1160 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID NO:394).

In yet another aspect, the invention concerns an isolated PRO1160 polypeptide, comprising the sequence of amino acid residues 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID NO:394), or a fragment thereof sufficient to provide a binding site for an anti-PRO1160 antibody. Preferably, the PRO1160 fragment retains a qualitative biological activity of a native PRO1160 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1160 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 90, inclusive of Figure 282 (SEQ ID NO:394), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a



90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

124. **PRO1187**

5 A cDNA clone (DNA62876-1517) has been identified that encodes a novel polypeptide having sequence identity with endo-beta-1,4-xylanase and designated in the present application as "PRO1187."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1187 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1187 polypeptide having the sequence of amino acid residues from about 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1187 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 172 and about 480, inclusive, of Figure 283 (SEQ ID NO:398). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203095 (DNA62876-1517), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203095 (DNA62876-1517).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1187 polypeptide having the sequence of amino acid residues from about 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35



In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1187 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 through about 80 nucleotides in length, preferably from about 20 through about 60 nucleotides in length, more preferably from about 20 through about 50 nucleotides in length, and most preferably from about 20 through about 40 nucleotides in length.

10 In another embodiment, the invention provides isolated PRO1187 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1187 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 18 through 120 of Figure 284 (SEQ ID NO:399).

15 In another aspect, the invention concerns an isolated PRO1187 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399).

20 In a further aspect, the invention concerns an isolated PRO1187 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 18 through 120 of Figure 284 (SEQ ID NO:399).

25 In yet another aspect, the invention concerns an isolated PRO1187 polypeptide, comprising the sequence of amino acid residues 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399), or a fragment thereof sufficient to provide a binding site for an anti-PRO1187 antibody. Preferably, the PRO1187 fragment retains a qualitative biological activity of a native PRO1187 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1187 polypeptide having the sequence of amino acid residues from about 18 to about 120, inclusive of Figure 284 (SEQ ID NO:399), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1187 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1187 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1187 polypeptide, by contacting the native PRO1187 polypeptide with a candidate molecule and

monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1187 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**125. PRO1185**

5 A cDNA clone (DNA62881-1515) has been identified that encodes a novel polypeptide having sequence identity to a glucose repression regulatory protein, tup1, and designated in the present application as "PRO1185."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1185 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1185 polypeptide having the sequence of amino acid residues from about 22 to about 198, inclusive of Figure 286 (SEQ ID NO:401), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1185 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 67 and about 597, inclusive, of Figure 285 (SEQ ID NO:400). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
20 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203096 (DNA62881-1515), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
25 Deposit No. 203096 (DNA62881-1515).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 22 to about 198, inclusive of Figure 286 (SEQ ID  
30 NO:401), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1185 polypeptide having the sequence of amino acid residues from about 22 to about 198, inclusive of Figure 286 (SEQ ID NO:401), or (b)  
35 the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 22 to about 198, inclusive of Figure 286 (SEQ ID NO:401), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1185 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 through about 80 nucleotides in length, preferably from about 20 through about 60 nucleotides in length, more preferably from about 20 through about 50 nucleotides in length, and most preferably from about 20 through about 40 nucleotides in length.

10 In another embodiment, the invention provides isolated PRO1185 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1185 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 22 through 198 of Figure 286 (SEQ ID NO:401).

15 In another aspect, the invention concerns an isolated PRO1185 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 22 to about 198, inclusive of Figure 286 (SEQ ID NO:401).

20 In a further aspect, the invention concerns an isolated PRO1185 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 22 through 198 of Figure 286 (SEQ ID NO:401).

25 In yet another aspect, the invention concerns an isolated PRO1185 polypeptide, comprising the sequence of amino acid residues 22 to about 198, inclusive of Figure 286 (SEQ ID NO:401), or a fragment thereof sufficient to provide a binding site for an anti-PRO1185 antibody. Preferably, the PRO1185 fragment retains a qualitative biological activity of a native PRO1185 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1185 polypeptide having the sequence of amino acid residues from about 22 to about 198, inclusive of Figure 286 (SEQ ID NO:401), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1185 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1185 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1185 polypeptide, by contacting the native PRO1185 polypeptide with a candidate molecule and

monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1185 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**126. PRO1345**

5 A cDNA clone (DNA64852-1589) has been identified, having homology to nucleic acid encoding tetranectin protein that encodes a novel polypeptide, designated in the present application as "PRO1345".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1345 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1345 polypeptide having the sequence of amino acid residues from about 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1345 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 7 or about 100 and about 624, inclusive, of Figure 287 (SEQ ID NO:402). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203127 (DNA64852-1589) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203127 (DNA64852-1589).

25 In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403), or (b) the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1345 polypeptide having the sequence of amino acid residues from 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

35



In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1345 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 or amino acid 10 to about amino acid position 31 in the sequence of Figure 288 (SEQ ID NO:403).

5 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403), or (b) the complement of the DNA of (a).

10 Another embodiment is directed to fragments of a PRO1345 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 287 (SEQ ID NO:402).

15 In another embodiment, the invention provides isolated PRO1345 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1345 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 32 to about 206 of Figure 288 (SEQ ID NO:403).

20 In another aspect, the invention concerns an isolated PRO1345 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403).

25 In a further aspect, the invention concerns an isolated PRO1345 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403).

30 In yet another aspect, the invention concerns an isolated PRO1345 polypeptide, comprising the sequence of amino acid residues 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403), or a fragment thereof sufficient to provide a binding site for an anti-PRO1345 antibody. Preferably, the PRO1345 fragment retains a qualitative biological activity of a native PRO1345 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1345 polypeptide having the sequence of amino acid residues from about 1 or about 32 to about 206, inclusive of Figure 288 (SEQ ID NO:403), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host

cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1345 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1345 antibody.

5 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1345 polypeptide by contacting the native PRO1345 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1345 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

10 127. **PRO1245**

A cDNA clone (DNA64884-1527) has been identified that encodes a novel secreted polypeptide designated in the present application as "PRO1245."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1245 polypeptide.

15 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1245 polypeptide having the sequence of amino acid residues from about 19 to about 104, inclusive of Figure 290 (SEQ ID NO:408), or (b) the complement of the DNA molecule of (a).

20 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1245 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 133 and about 390, inclusive, of Figure 289 (SEQ ID NO:407). Preferably, hybridization occurs under stringent hybridization and wash conditions.

25 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203155 (DNA64884-1245), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC  
30 Deposit No. 203155 (DNA64884-1245).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 19 to about 104, inclusive of Figure 290 (SEQ ID  
35 NO:408), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule

under stringent conditions with (a) a DNA molecule encoding a PRO1245 polypeptide having the sequence of amino acid residues from about 19 to about 104, inclusive of Figure 290 (SEQ ID NO:408), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

5 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1245 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 18 in the sequence of Figure 290 (SEQ ID NO:408).

10 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 19 to about 104, inclusive of Figure 290 (SEQ ID NO:408), or (b) the complement of the DNA of (a).

15 Another embodiment is directed to fragments of a PRO1245 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1245 polypeptide encoded by any of the  
20 isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1245 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 19 to 104 of Figure 290 (SEQ ID NO:408).

In another aspect, the invention concerns an isolated PRO1245 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more  
25 preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 19 to about 104, inclusive of Figure 290 (SEQ ID NO:408).

In a further aspect, the invention concerns an isolated PRO1245 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence  
30 of residues 19 to 104 of Figure 290 (SEQ ID NO:408).

In yet another aspect, the invention concerns an isolated PRO1245 polypeptide, comprising the sequence of amino acid residues 19 to about 104, inclusive of Figure 290 (SEQ ID NO:408), or a fragment thereof sufficient to provide a binding site for an anti-PRO1245 antibody. Preferably, the PRO1245 fragment retains a qualitative biological activity of a native PRO1245 polypeptide.

35 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1245 polypeptide having the sequence of amino acid residues from about 19 to about 104, inclusive of Figure 290 (SEQ ID NO:408), or (b)



the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

5  
128. **PRO1358**

A cDNA clone (DNA64890-1612) has been identified that encodes a novel polypeptide having sequence identity with RASP-1 and designated in the present application as "PRO1358."

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1358 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1358 polypeptide having the sequence of amino acid residues from about 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1358 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 140 and about 1417, inclusive, of Figure 292 (SEQ ID NO:410). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203131 (DNA64890-1612), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic  
25 acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203131 (DNA64890-1612).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1358 polypeptide having the sequence of  
35 amino acid residues from about 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most



preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1358 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 80 nucleotides to about 120 nucleotides in length.

In another embodiment, the invention provides isolated PRO1358 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1358 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 19 through 444 of Figure 292 (SEQ ID NO:410).

In another aspect, the invention concerns an isolated PRO1358 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410).

In a further aspect, the invention concerns an isolated PRO1358 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 19 through 444 of Figure 292 (SEQ ID NO:410).

In yet another aspect, the invention concerns an isolated PRO1358 polypeptide, comprising the sequence of amino acid residues 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410), or a fragment thereof sufficient to provide a binding site for an anti-PRO1358 antibody specific therefore. Preferably, the PRO1358 fragment retains a qualitative biological activity of a native PRO1358 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1358 polypeptide having the sequence of amino acid residues from about 19 to about 444, inclusive of Figure 292 (SEQ ID NO:410), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1358 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1358 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1358 polypeptide, by contacting the native PRO1358 polypeptide with a candidate molecule and

monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1358 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**129. PRO1195**

5 A cDNA clone (DNA65412-1523) has been identified that encodes a novel polypeptide having sequence identity with a mouse proline rich acidic protein and designated in the present application as "PRO1195."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1195 polypeptide.

10 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1195 polypeptide having the sequence of amino acid residues from about 23 to about 151, inclusive of Figure 294 (SEQ ID NO:412), or (b) the complement of the DNA molecule of (a).

15 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1195 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 124 and about 510, inclusive, of Figure 293 (SEQ ID NO:411). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203094 (DNA65412-1523), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203094 (DNA65412-1523).

25 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 23 to about 151, inclusive of Figure 294 (SEQ ID NO:412), or the complement of the DNA of (a).

30 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1195 polypeptide having the sequence of amino acid residues from about 23 to about 151, inclusive of Figure 294 (SEQ ID NO:412), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, 35 preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 to about 151, inclusive of Figure 294 (SEQ ID NO:412), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1195 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 through about 80 nucleotides in length, preferably from about 20 through about 60 nucleotides in length, more preferably from about 20 through about 50 nucleotides in length, and most preferably from about 20 through about 40 nucleotides in length.

10 In another embodiment, the invention provides isolated PRO1195 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1195 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 23 through 151 of Figure 294 (SEQ ID NO:412).

15 In another aspect, the invention concerns an isolated PRO1195 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 23 to about 151, inclusive of Figure 294 (SEQ ID NO:412).

20 In a further aspect, the invention concerns an isolated PRO1195 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 23 through 151 of Figure 294 (SEQ ID NO:412).

25 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1195 polypeptide having the sequence of amino acid residues from about 23 to about 151, inclusive of Figure 294 (SEQ ID NO:412), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

30 In yet another embodiment, the invention concerns agonists and antagonists of the a native PRO1195 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1195 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1195 polypeptide, by contacting the native PRO1195 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

35 In a still further embodiment, the invention concerns a composition comprising a PRO1195 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

**130. PRO1270**

A cDNA clone (DNA66308-1537) has been identified, having homology to nucleic acid encoding a lectin protein, that encodes a novel polypeptide, designated in the present application as "PRO1270".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1270 polypeptide.

5 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1270 polypeptide having the sequence of amino acid residues from about 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414), or (b) the complement of the DNA molecule of (a).

10 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1270 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 103 or about 151 and about 1041, inclusive, of Figure 295 (SEQ ID NO:413). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
15 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203159 (DNA66308-1537) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
20 ATCC Deposit No. 203159 (DNA66308-1537).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID  
25 NO:414), or (b) the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 285 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1270 polypeptide having the sequence of amino acid residues from 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414), or (b) the complement of the DNA molecule of (a), and,  
30 if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1270 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is  
35 complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 16 in the sequence of Figure 296 (SEQ ID NO:414).



In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414), or (b) the complement of the DNA of (a).

5 Another embodiment is directed to fragments of a PRO1270 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 295 (SEQ ID NO:413).

10 In another embodiment, the invention provides isolated PRO1270 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1270 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 17 to about 313 of Figure 296 (SEQ ID NO:414).

15 In another aspect, the invention concerns an isolated PRO1270 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414).

20 In a further aspect, the invention concerns an isolated PRO1270 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414).

25 In yet another aspect, the invention concerns an isolated PRO1270 polypeptide, comprising the sequence of amino acid residues 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414), or a fragment thereof sufficient to provide a binding site for an anti-PRO1270 antibody. Preferably, the PRO1270 fragment retains a qualitative biological activity of a native PRO1270 polypeptide.

30 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1270 polypeptide having the sequence of amino acid residues from about 1 or about 17 to about 313, inclusive of Figure 296 (SEQ ID NO:414), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

35 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1270 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1270 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1270 polypeptide by contacting the native PRO1270 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1270 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

5  
131. **PRO1271**

A cDNA clone (DNA66309-1538) has been identified that encodes a novel polypeptide having serine and threonine rich regions designated in the present application as "PRO1271" polypeptides.

10 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1271 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1271 polypeptide having the sequence of amino acid residues from about 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416), or  
15 (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1271 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 187 and about 717, inclusive, of Figure 297 (SEQ ID NO:415). Preferably, hybridization occurs under stringent hybridization and wash conditions.

20 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203235 (DNA66309-1538), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic  
25 acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203235 (DNA66309-1538).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence  
30 identity to the sequence of amino acid residues from about 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416), or the complement of the DNA of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1271 polypeptide having the sequence of  
35 amino acid residues from about 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most

preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1271 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e. transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from amino acid position 1 through about amino acid position 31 in the sequence of Figure 298 (SEQ ID NO:416). The transmembrane domain has been tentatively identified as extending from about amino acid position 166 through about amino acid position 187 in the PRO1271 amino acid sequence (Figure 298, SEQ ID NO:416).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1271 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1271 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1271 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 32 through 208 of Figure 298 (SEQ ID NO:416).

In another aspect, the invention concerns an isolated PRO1271 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416).

In a further aspect, the invention concerns an isolated PRO1271 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 32 through 208 of Figure 298 (SEQ ID NO:416).

In yet another aspect, the invention concerns an isolated PRO1271 polypeptide, comprising the sequence of amino acid residues 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416), or a fragment thereof sufficient to provide a binding site for an anti-PRO1271 antibody. Preferably, the PRO1271 fragment retains a qualitative biological activity of a native PRO1271 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1271 polypeptide having the sequence of amino acid residues from about 32 to about 208, inclusive of Figure 298 (SEQ ID NO:416), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence

identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1271 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1271 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1271 polypeptide, by contacting the native PRO1271 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1271 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 132. PRO1375

A cDNA clone (DNA67004-1614) has been identified that encodes a novel polypeptide having sequence identity with PUT2 and designated in the present application as "PRO1375."

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1375 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1375 polypeptide having the sequence of amino acid residues from about 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1375 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 104 and about 697, inclusive, of Figure 299 (SEQ ID NO:417). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203115 (DNA67004-1614), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203115 (DNA67004-1614).

In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418), or the complement of the DNA of (a).



In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1375 polypeptide having the sequence of amino acid residues from about 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1375 polypeptide in its soluble form, i.e. transmembrane domains deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The transmembrane domains have been tentatively identified as at about amino acid positions 11-28 (type II) and 103-125 of SEQ ID NO:418.

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1375 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1375 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1375 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 through 198 of Figure 300 (SEQ ID NO:418).

In another aspect, the invention concerns an isolated PRO1375 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418).

In a further aspect, the invention concerns an isolated PRO1375 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 through 198 of Figure 300 (SEQ ID NO:418).

In yet another aspect, the invention concerns an isolated PRO1375 polypeptide, comprising the sequence of amino acid residues 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418), or a fragment thereof sufficient to provide a binding site for an anti-PRO1375 antibody. Preferably, the PRO1375 fragment retains a qualitative biological activity of a native PRO1375 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1375 polypeptide having the sequence of amino acid residues from about 1 to about 198, inclusive of Figure 300 (SEQ ID NO:418), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1375 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1375 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1375 polypeptide, by contacting the native PRO1375 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1375 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 133. PRO1385

A cDNA clone (DNA68869-1610) has been identified that encodes a novel secreted polypeptide, designated in the present application as "PRO1385".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1385 polypeptide.

In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1385 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420), or (b) the complement of the DNA molecule of (a).

In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1385 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 26 or about 110 and about 409, inclusive, of Figure 301 (SEQ ID NO:419). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203164 (DNA68869-1610) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203164 (DNA68869-1610).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420), or (b) the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 245 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1385 polypeptide having the sequence of amino acid residues from 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80 % sequence identity, preferably at least about an 85% sequence  
10 identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1385 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as  
15 extending from about amino acid position 1 to about amino acid position 28 in the sequence of Figure 302 (SEQ ID NO:420).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the  
20 amino acid sequence of residues 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1385 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50  
25 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 301 (SEQ ID NO:419).

In another embodiment, the invention provides isolated PRO1385 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a specific aspect, the invention provides isolated native sequence PRO1385 polypeptide, which in  
30 certain embodiments, includes an amino acid sequence comprising residues 1 or about 29 to about 128 of Figure 302 (SEQ ID NO:420).

In another aspect, the invention concerns an isolated PRO1385 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the  
35 sequence of amino acid residues 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420).

In a further aspect, the invention concerns an isolated PRO1385 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least

about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420).

In yet another aspect, the invention concerns an isolated PRO1385 polypeptide, comprising the sequence of amino acid residues 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420), or a fragment thereof sufficient to provide a binding site for an anti-PRO1385 antibody. Preferably, the PRO1385 fragment  
5 retains a qualitative biological activity of a native PRO1385 polypeptide.

In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1385 polypeptide having the sequence of amino acid residues from about 1 or about 29 to about 128, inclusive of Figure 302 (SEQ ID NO:420), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about  
10 an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

15 **134. PRO1387**

A cDNA clone (DNA68872-1620) has been identified, having homology to nucleic acid encoding myelin, that encodes a novel polypeptide, designated in the present application as "PRO1387".

In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1387 polypeptide.

20 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1387 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422), or (b) the complement of the DNA molecule of (a).

25 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1387 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about nucleotides 85 or about 142 and about 1266, inclusive, of Figure 303 (SEQ ID NO:421). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having  
30 at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203160 (DNA68872-1620) or (b) the complement of the nucleic acid molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in  
35 ATCC Deposit No. 203160 (DNA68872-1620).

In still a further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence



identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422), or (b) the complement of the DNA of (a).

5 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least 395 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1387 polypeptide having the sequence of amino acid residues from 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

10 In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1387 polypeptide, with or without the N-terminal signal sequence and/or the initiating methionine, and its soluble, i.e., transmembrane domain deleted or inactivated variants, or is complementary to such encoding nucleic acid molecule. The signal peptide has been tentatively identified as extending from about amino acid position 1 to about amino acid position 19 in the sequence of Figure 304 (SEQ ID NO:422). The transmembrane domain has been tentatively identified as extending from about amino acid position 275 to about amino acid position 296 in the PRO1387 amino acid sequence (Figure 304, SEQ ID NO:422).

15 In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422), or (b) the complement of the DNA of (a).

20 Another embodiment is directed to fragments of a PRO1387 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 nucleotides in length and most preferably from about 20 to about 40 nucleotides in length and may be derived from the nucleotide sequence shown in Figure 303 (SEQ ID NO:421).

In another embodiment, the invention provides isolated PRO1387 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

25 In a specific aspect, the invention provides isolated native sequence PRO1387 polypeptide, which in certain embodiments, includes an amino acid sequence comprising residues 1 or about 20 to about 394 of Figure 304 (SEQ ID NO:422).

30 In another aspect, the invention concerns an isolated PRO1387 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422).

35 In a further aspect, the invention concerns an isolated PRO1387 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least

about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422).

5 In yet another aspect, the invention concerns an isolated PRO1387 polypeptide, comprising the sequence of amino acid residues 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422), or a fragment thereof sufficient to provide a binding site for an anti-PRO1387 antibody. Preferably, the PRO1387 fragment retains a qualitative biological activity of a native PRO1387 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1387 polypeptide having the sequence of amino acid residues from about 1 or about 20 to about 394, inclusive of Figure 304 (SEQ ID NO:422), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

15 In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1387 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1387 antibody.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1387 polypeptide by contacting the native PRO1387 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

20 In a still further embodiment, the invention concerns a composition comprising a PRO1387 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 135. PRO1384

A cDNA clone, referred to herein as "DNA71159", has been identified that encodes a novel polypeptide having homology to NKG2-D protein designated in the present application as "PRO1384".

25 In one embodiment, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1384 polypeptide.

30 In one aspect, the isolated nucleic acid comprises DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding a PRO1384 polypeptide having the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or (b) the complement of the DNA molecule of (a).

35 In another aspect, the invention concerns an isolated nucleic acid molecule encoding a PRO1384 polypeptide comprising DNA hybridizing to the complement of the nucleic acid between about residues 182 and about 868, inclusive, of Figure 305 (SEQ ID NO:423). Preferably, hybridization occurs under stringent hybridization and wash conditions.

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising DNA having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least

about 90% sequence identity, most preferably at least about 95% sequence identity to (a) a DNA molecule encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203135 (DNA71159-1617), or (b) the complement of the DNA molecule of (a). In a preferred embodiment, the nucleic acid comprises a DNA encoding the same mature polypeptide encoded by the human protein cDNA in ATCC Deposit No. 203135 (DNA71159-1617).

5 In a still further aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or the complement of the DNA of (a).

10 In a further aspect, the invention concerns an isolated nucleic acid molecule having at least about 50 nucleotides, and preferably at least about 100 nucleotides and produced by hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1384 polypeptide having the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or (b) the complement of the DNA molecule of (a), and, if the DNA molecule has at least about an 80% sequence identity, 15 preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), isolating the test DNA molecule.

In a specific aspect, the invention provides an isolated nucleic acid molecule comprising DNA encoding a PRO1384 polypeptide with its transmembrane domain deleted or inactivated, or is complementary to such encoding nucleic acid molecule. The transmembrane domain has been tentatively identified as extending from 20 about amino acid position 32 through about amino acid position 57 in the PRO1384 amino acid sequence (Figure 306, SEQ ID NO:424).

In another aspect, the invention concerns an isolated nucleic acid molecule comprising (a) DNA encoding a polypeptide scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the 25 amino acid sequence of residues 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or (b) the complement of the DNA of (a).

Another embodiment is directed to fragments of a PRO1384 polypeptide coding sequence that may find use as hybridization probes. Such nucleic acid fragments are from about 20 to about 80 nucleotides in length, preferably from about 20 to about 60 nucleotides in length, more preferably from about 20 to about 50 30 nucleotides in length, and most preferably from about 20 to about 40 nucleotides in length.

In another embodiment, the invention provides isolated PRO1384 polypeptide encoded by any of the isolated nucleic acid sequences hereinabove defined.

In a specific aspect, the invention provides isolated native sequence PRO1384 polypeptide, which in one embodiment, includes an amino acid sequence comprising residues 1 to 229 of Figure 306 (SEQ ID NO:424).

35 In another aspect, the invention concerns an isolated PRO1384 polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 85% sequence identity, more preferably at least about 90% sequence identity, most preferably at least about 95% sequence identity to the

sequence of amino acid residues 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424).

In a further aspect, the invention concerns an isolated PRO1384 polypeptide, comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 85% positives, more preferably at least about 90% positives, most preferably at least about 95% positives when compared with the amino acid sequence of residues 1 to 229 of Figure 306 (SEQ ID NO:424).

5 In yet another aspect, the invention concerns an isolated PRO1384 polypeptide, comprising the sequence of amino acid residues 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or a fragment thereof sufficient to provide a binding site for an anti-PRO1384 antibody. Preferably, the PRO1384 fragment retains a qualitative biological activity of a native PRO1384 polypeptide.

10 In a still further aspect, the invention provides a polypeptide produced by (i) hybridizing a test DNA molecule under stringent conditions with (a) a DNA molecule encoding a PRO1384 polypeptide having the sequence of amino acid residues from about 1 to about 229, inclusive of Figure 306 (SEQ ID NO:424), or (b) the complement of the DNA molecule of (a), and if the test DNA molecule has at least about an 80% sequence identity, preferably at least about an 85% sequence identity, more preferably at least about a 90% sequence identity, most preferably at least about a 95% sequence identity to (a) or (b), (ii) culturing a host cell comprising  
15 the test DNA molecule under conditions suitable for expression of the polypeptide, and (iii) recovering the polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO1384 polypeptide. In a particular embodiment, the agonist or antagonist is an anti-PRO1384 antibody.

20 In a further embodiment, the invention concerns a method of identifying agonists or antagonists of a native PRO1384 polypeptide, by contacting the native PRO1384 polypeptide with a candidate molecule and monitoring a biological activity mediated by said polypeptide.

In a still further embodiment, the invention concerns a composition comprising a PRO1384 polypeptide, or an agonist or antagonist as hereinabove defined, in combination with a pharmaceutically acceptable carrier.

### 25 136. Additional Embodiments

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the above or below described polypeptides. A host cell comprising any such vector is also provided. By way of example, the host cells may be CHO cells, *E. coli*, or yeast. A process for producing any of the above or below described polypeptides is further provided and comprises culturing host cells under  
30 conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the above or below described polypeptides fused to a heterologous polypeptide or amino acid sequence. An example of such a chimeric molecule comprises any of the above or below described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.  
35

In another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody.



In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences, wherein those probes may be derived from any of the above or below described nucleotide sequences.

In other embodiments, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

5 In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a full-length amino acid sequence lacking the signal peptide as disclosed herein or an extracellular domain of a transmembrane protein as disclosed herein, or (b) the complement of the DNA molecule of (a).

20 In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) a DNA molecule having the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a full-length PRO polypeptide lacking the signal peptide as disclosed herein or the coding sequence of an extracellular domain of a transmembrane PRO polypeptide as disclosed herein, or (b) the complement of the DNA molecule of (a).

35 In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence

identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence that may find use as, for example, hybridization probes or for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody. Such nucleic acid fragments are usually at least about 20 nucleotides in length, preferably at least about 30 nucleotides in length, more preferably at least about 40 nucleotides in length, yet more preferably at least about 50 nucleotides in length, yet more preferably at least about 60 nucleotides in length, yet more preferably at least about 70 nucleotides in length, yet more preferably at least about 80 nucleotides in length, yet more preferably at least about 90 nucleotides in length, yet more preferably at least about 100 nucleotides in length, yet more preferably at least about 110 nucleotides in length, yet more preferably at least about 120 nucleotides in length, yet more preferably at least about 130 nucleotides in length, yet more preferably at least about 140 nucleotides in length, yet more preferably at least about 150 nucleotides in length, yet more preferably at least about 160 nucleotides in length, yet more preferably at least about 170 nucleotides in length, yet more preferably at least about 180 nucleotides in length, yet more preferably at least about 190 nucleotides in length, yet more preferably at least about 200 nucleotides in length, yet more preferably at least about 250 nucleotides in length, yet more preferably at least about 300 nucleotides in length, yet more preferably at least about 350 nucleotides in length, yet more preferably at least about 400 nucleotides in length, yet more preferably at least about 450 nucleotides in length, yet more preferably at least about 500 nucleotides in length, yet more preferably at least about 600 nucleotides in length, yet more preferably at least about 700 nucleotides in length, yet more preferably at least about 800 nucleotides in length, yet more preferably at least about 900 nucleotides in length and yet more preferably at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide

sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

5 In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

10 In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a full-length amino acid sequence lacking the signal peptide as disclosed herein or an extracellular domain of a transmembrane protein as disclosed herein.

20 In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about 80% sequence identity, preferably at least about 81% sequence identity, more preferably at least about 82% sequence identity, yet more preferably at least about 83% sequence identity, yet more preferably at least about 84% sequence identity, yet more preferably at least about 85% sequence identity, yet more preferably at least about 86% sequence identity, yet more preferably at least about 87% sequence identity, yet more preferably at least about 88% sequence identity, yet more preferably at least about 89% sequence identity, yet more preferably at least about 90% sequence identity, yet more preferably at least about 91% sequence identity, yet more preferably at least about 92% sequence identity, yet more preferably at least about 93% sequence identity, yet more preferably at least about 94% sequence identity, yet more preferably at least about 95% sequence identity, yet more preferably at least about 96% sequence identity, yet more preferably at least about 97% sequence identity, yet more preferably at least about 98% sequence identity and yet more preferably at least about 99% sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

30 In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence scoring at least about 80% positives, preferably at least about 81% positives, more preferably at least about 82% positives, yet more preferably at least about 83% positives, yet more preferably at least about 84% positives, yet more preferably at least about 85% positives, yet more preferably at least about 86% positives,



yet more preferably at least about 87% positives, yet more preferably at least about 88% positives, yet more preferably at least about 89% positives, yet more preferably at least about 90% positives, yet more preferably at least about 91% positives, yet more preferably at least about 92% positives, yet more preferably at least about 93% positives, yet more preferably at least about 94% positives, yet more preferably at least about 95% positives, yet more preferably at least about 96% positives, yet more preferably at least about 97% positives, yet more preferably at least about 98% positives and yet more preferably at least about 99% positives when compared with the amino acid sequence of a PRO polypeptide having a full-length amino acid sequence as disclosed herein, a full-length amino acid sequence lacking the signal peptide as disclosed herein or an extracellular domain of a transmembrane protein as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO281 (UNQ244) cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA16422-1209".

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO276 (UNQ243) cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA16435-1208".

Figure 4 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO189 (UNQ163) cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA21642-1391".

Figure 6 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 5.



Figure 7 shows a nucleotide sequence designated herein as DNA14187 (SEQ ID NO:9).

Figure 8 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO190 (UNQ164) cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA23334-1392".

Figure 9 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 8.

5 Figure 10 shows a nucleotide sequence designated herein as DNA14232 (SEQ ID NO:15).

Figure 11 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO341 (UNQ300) cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA26288-1239".

Figure 12 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 11.

10 Figure 13 shows a nucleotide sequence designated herein as DNA12920 (SEQ ID NO:21).

Figure 14 shows a nucleotide sequence (SEQ ID NO:22) of a native sequence PRO180 (UNQ154) cDNA, wherein SEQ ID NO:22 is a clone designated herein as "DNA26843-1389".

Figure 15 shows the amino acid sequence (SEQ ID NO:23) derived from the coding sequence of SEQ ID NO:22 shown in Figure 14.

15 Figure 16 shows a nucleotide sequence designated herein as DNA12922 (SEQ ID NO:24).

Figure 17 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO194 (UNQ168) cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA26844-1394".

Figure 18 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 17.

20 Figure 19 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO203 (UNQ177) cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA30862-1396".

Figure 20 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 19.

Figure 21 shows a nucleotide sequence designated herein as DNA15618 (SEQ ID NO:31).

25 Figure 22 shows a nucleotide sequence (SEQ ID NO:32) of a native sequence PRO290 (UNQ253) cDNA, wherein SEQ ID NO:32 is a clone designated herein as "DNA35680-1212".

Figure 23 shows the amino acid sequence (SEQ ID NO:33) derived from the coding sequence of SEQ ID NO:32 shown in Figure 22.

30 Figure 24 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO874 (UNQ441) cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA40621-1440".

Figure 25 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 24.

Figure 26 shows a nucleotide sequence (SEQ ID NO:40) of a native sequence PRO710 (UNQ374) cDNA, wherein SEQ ID NO:40 is a clone designated herein as "DNA44161-1434".

35 Figure 27 shows the amino acid sequence (SEQ ID NO:41) derived from the coding sequence of SEQ ID NO:40 shown in Figure 26.

Figure 28 shows a nucleotide sequence designated herein as DNA38190 (SEQ ID NO:42).

Figure 29 shows a nucleotide sequence (SEQ ID NO:46) of a native sequence PRO1151 (UNQ581) cDNA, wherein SEQ ID NO:46 is a clone designated herein as "DNA44694-1500".

Figure 30 shows the amino acid sequence (SEQ ID NO:47) derived from the coding sequence of SEQ ID NO:46 shown in Figure 29.

5 Figure 31 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO1282 (UNQ652) cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA45495-1550".

Figure 32 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:56) of a native sequence PRO358 cDNA, wherein SEQ ID NO:56 is a clone designated herein as "DNA47361-1154".

10 Figure 34 shows the amino acid sequence (SEQ ID NO:57) derived from the coding sequence of SEQ ID NO:56 shown in Figure 33.

Figures 35A-B show a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO1310 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA47394-1572".

15 Figure 36 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figures 35A-B.

Figure 37 shows a nucleotide sequence (SEQ ID NO:66) of a native sequence PRO698 (UNQ362) cDNA, wherein SEQ ID NO:66 is a clone designated herein as "DNA48320-1433".

Figure 38 shows the amino acid sequence (SEQ ID NO:67) derived from the coding sequence of SEQ ID NO:66 shown in Figure 37.

20 Figure 39 shows a nucleotide sequence designated herein as DNA39906 (SEQ ID NO:68).

Figure 40 shows a nucleotide sequence (SEQ ID NO:72) of a native sequence PRO732 (UNQ396) cDNA, wherein SEQ ID NO:72 is a clone designated herein as "DNA48334-1435".

Figure 41 shows the amino acid sequence (SEQ ID NO:73) derived from the coding sequence of SEQ ID NO:72 shown in Figure 40.

25 Figure 42 shows a nucleotide sequence designated herein as DNA20239 (SEQ ID NO:74).

Figure 43 shows a nucleotide sequence designated herein as DNA38050 (SEQ ID NO:75).

Figure 44 shows a nucleotide sequence designated herein as DNA40683 (SEQ ID NO:76).

Figure 45 shows a nucleotide sequence designated herein as DNA42580 (SEQ ID NO:77).

30 Figures 46A-B show a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO1120 (UNQ559) cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA48606-1479".

Figure 47 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID NO:83 shown in Figures 46A-B.

Figure 48 shows a nucleotide sequence (SEQ ID NO:94) of a native sequence PRO537 (UNQ338) cDNA, wherein SEQ ID NO:94 is a clone designated herein as "DNA49141-1431".

35 Figure 49 shows the amino acid sequence (SEQ ID NO:95) derived from the coding sequence of SEQ ID NO:94 shown in Figure 48.

Figure 50 shows a nucleotide sequence (SEQ ID NO:96) of a native sequence PRO536 (UNQ337)

cDNA, wherein SEQ ID NO:96 is a clone designated herein as "DNA49142-1430".

Figure 51 shows the amino acid sequence (SEQ ID NO:97) derived from the coding sequence of SEQ ID NO:96 shown in Figure 50.

Figure 52 shows a nucleotide sequence (SEQ ID NO:98) of a native sequence PRO535 (UNQ336) cDNA, wherein SEQ ID NO:98 is a clone designated herein as "DNA49143-1429".

5 Figure 53 shows the amino acid sequence (SEQ ID NO:99) derived from the coding sequence of SEQ ID NO:98 shown in Figure 52.

Figure 54 shows a nucleotide sequence designated herein as DNA30861 (SEQ ID NO:100).

Figure 55 shows a nucleotide sequence designated herein as DNA36351 (SEQ ID NO:101).

10 Figure 56 shows a nucleotide sequence (SEQ ID NO:102) of a native sequence PRO718 (UNQ386) cDNA, wherein SEQ ID NO:102 is a clone designated herein as "DNA49647-1398".

Figure 57 shows the amino acid sequence (SEQ ID NO:103) derived from the coding sequence of SEQ ID NO:102 shown in Figure 56.

Figure 58 shows a nucleotide sequence designated herein as DNA15386 (SEQ ID NO:104).

Figure 59 shows a nucleotide sequence designated herein as DNA16630 (SEQ ID NO:105).

15 Figure 60 shows a nucleotide sequence designated herein as DNA16829 (SEQ ID NO:106).

Figure 61 shows a nucleotide sequence designated herein as DNA28357 (SEQ ID NO:107).

Figure 62 shows a nucleotide sequence designated herein as DNA43512 (SEQ ID NO:108).

Figure 63 shows a nucleotide sequence (SEQ ID NO:112) of a native sequence PRO872 (UNQ439) cDNA, wherein SEQ ID NO:112 is a clone designated herein as "DNA49819-1439".

20 Figure 64 shows the amino acid sequence (SEQ ID NO:113) derived from the coding sequence of SEQ ID NO:112 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:114) of a native sequence PRO1063 (UNQ128) cDNA, wherein SEQ ID NO:114 is a clone designated herein as "DNA49820-1427".

25 Figure 66 shows the amino acid sequence (SEQ ID NO:115) derived from the coding sequence of SEQ ID NO:114 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:116) of a native sequence PRO619 (UNQ355) cDNA, wherein SEQ ID NO:116 is a clone designated herein as "DNA49821-1562".

Figure 68 shows the amino acid sequence (SEQ ID NO:117) derived from the coding sequence of SEQ ID NO:116 shown in Figure 67.

30 Figure 69 shows a nucleotide sequence (SEQ ID NO:118) of a native sequence PRO943 (UNQ480) cDNA, wherein SEQ ID NO:118 is a clone designated herein as "DNA52192-1369".

Figure 70 shows the amino acid sequence (SEQ ID NO:119) derived from the coding sequence of SEQ ID NO:118 shown in Figure 69.

35 Figure 71 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO1188 (UNQ602) cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA52598-1518".

Figure 72 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 71.

Figure 73 shows a nucleotide sequence (SEQ ID NO:128) of a native sequence PRO1133 (UNQ571) cDNA, wherein SEQ ID NO:128 is a clone designated herein as "DNA53913-1490".

Figure 74 shows the amino acid sequence (SEQ ID NO:129) derived from the coding sequence of SEQ ID NO:128 shown in Figure 73.

Figure 75 shows a nucleotide sequence (SEQ ID NO:134) of a native sequence PRO784 (UNQ459) cDNA, wherein SEQ ID NO:134 is a clone designated herein as "DNA53978-1443".

Figure 76 shows the amino acid sequence (SEQ ID NO:135) derived from the coding sequence of SEQ ID NO:134 shown in Figure 75.

Figure 77 shows a nucleotide sequence designated herein as DNA44661 (SEQ ID NO:136).

Figure 78 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO783 (UNQ458) cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA53996-1442".

Figure 79 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 78.

Figure 80 shows a nucleotide sequence designated herein as DNA45201 (SEQ ID NO:139).

Figure 81 shows a nucleotide sequence designated herein as DNA14575 (SEQ ID NO:140).

Figure 82 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO820 (UNQ503) cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA56041-1416".

Figure 83 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 82.

Figure 84 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO1080 (UNQ537)

cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA56047-1456".

Figure 85 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 84.

Figure 86 shows a nucleotide sequence designated herein as DNA36527 (SEQ ID NO:149).

Figure 87 shows a nucleotide sequence (SEQ ID NO:150) of a native sequence PRO1079 (UNQ536) cDNA, wherein SEQ ID NO:150 is a clone designated herein as "DNA56050-1455".

Figure 88 shows the amino acid sequence (SEQ ID NO:151) derived from the coding sequence of SEQ ID NO:150 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO:152) of a native sequence PRO793 (UNQ432) cDNA, wherein SEQ ID NO:152 is a clone designated herein as "DNA56110-1437".

Figure 90 shows the amino acid sequence (SEQ ID NO:153) derived from the coding sequence of SEQ ID NO:152 shown in Figure 89.

Figure 91 shows a nucleotide sequence designated herein as DNA50177 (SEQ ID NO:154).

Figure 92 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO1016 (UNQ499) cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA56113-1378".

Figure 93 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 92.



Figure 94 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO1013 (UNQ496) cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA56410-1414".

Figure 95 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ ID NO:157 shown in Figure 94.

5 Figure 96 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO937 (UNQ474) cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA56436-1448".

Figure 97 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 96.

Figure 98 shows a nucleotide sequence (SEQ ID NO:164) of a native sequence PRO842 (UNQ473) cDNA, wherein SEQ ID NO:164 is a clone designated herein as "DNA56855-1447".

10 Figure 99 shows the amino acid sequence (SEQ ID NO:165) derived from the coding sequence of SEQ ID NO:164 shown in Figure 98.

Figure 100 shows a nucleotide sequence (SEQ ID NO:166) of a native sequence PRO839 (UNQ472) cDNA, wherein SEQ ID NO:166 is a clone designated herein as "DNA56859-1445".

15 Figure 101 shows the amino acid sequence (SEQ ID NO:167) derived from the coding sequence of SEQ ID NO:166 shown in Figure 100.

Figure 102 shows a nucleotide sequence (SEQ ID NO:168) of a native sequence PRO1180 (UNQ594) cDNA, wherein SEQ ID NO:168 is a clone designated herein as "DNA56860-1510".

Figure 103 shows the amino acid sequence (SEQ ID NO:169) derived from the coding sequence of SEQ ID NO:168 shown in Figure 102.

20 Figure 104 shows a nucleotide sequence (SEQ ID NO:170) of a native sequence PRO1134 (UNQ572) cDNA, wherein SEQ ID NO:170 is a clone designated herein as "DNA56865-1491".

Figure 105 shows the amino acid sequence (SEQ ID NO:171) derived from the coding sequence of SEQ ID NO:170 shown in Figure 104.

Figure 106 shows a nucleotide sequence designated herein as DNA52352 (SEQ ID NO:172).

25 Figure 107 shows a nucleotide sequence designated herein as DNA55725 (SEQ ID NO:173).

Figure 108 shows a nucleotide sequence (SEQ ID NO:174) of a native sequence PRO830 (UNQ470) cDNA, wherein SEQ ID NO:174 is a clone designated herein as "DNA56866-1342".

Figure 109 shows the amino acid sequence (SEQ ID NO:175) derived from the coding sequence of SEQ ID NO:174 shown in Figure 108.

30 Figure 110 shows a nucleotide sequence (SEQ ID NO:176) of a native sequence PRO1115 (UNQ558) cDNA, wherein SEQ ID NO:176 is a clone designated herein as "DNA56868-1478".

Figure 111 shows the amino acid sequence (SEQ ID NO:177) derived from the coding sequence of SEQ ID NO:176 shown in Figure 110.

35 Figure 112 shows a nucleotide sequence (SEQ ID NO:178) of a native sequence PRO1277 (UNQ647) cDNA, wherein SEQ ID NO:178 is a clone designated herein as "DNA56869-1545".

Figure 113 shows the amino acid sequence (SEQ ID NO:179) derived from the coding sequence of SEQ ID NO:178 shown in Figure 112.

Figure 114 shows a nucleotide sequence (SEQ ID NO:180) of a native sequence PRO1135 (UNQ573) cDNA, wherein SEQ ID NO:180 is a clone designated herein as "DNA56870-1492".

Figure 115 shows the amino acid sequence (SEQ ID NO:181) derived from the coding sequence of SEQ ID NO:180 shown in Figure 114.

Figure 116 shows a nucleotide sequence (SEQ ID NO:182) of a native sequence PRO1114 (UNQ557) cDNA, wherein SEQ ID NO:182 is a clone designated herein as "DNA57033-1403".

Figure 117 shows the amino acid sequence (SEQ ID NO:183) derived from the coding sequence of SEQ ID NO:182 shown in Figure 116.

Figure 118 shows a nucleotide sequence designated herein as DNA48466 (SEQ ID NO:184).

Figure 119 shows a nucleotide sequence (SEQ ID NO:188) of a native sequence PRO828 (UNQ469) cDNA, wherein SEQ ID NO:188 is a clone designated herein as "DNA57037-1444".

Figure 120 shows the amino acid sequence (SEQ ID NO:189) derived from the coding sequence of SEQ ID NO:188 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:193) of a native sequence PRO1009 (UNQ493) cDNA, wherein SEQ ID NO:193 is a clone designated herein as "DNA57129-1413".

Figure 122 shows the amino acid sequence (SEQ ID NO:194) derived from the coding sequence of SEQ ID NO:193 shown in Figure 121.

Figure 123 shows a nucleotide sequence designated herein as DNA50853 (SEQ ID NO:195).

Figure 124 shows a nucleotide sequence (SEQ ID NO:196) of a native sequence PRO1007 (UNQ491) cDNA, wherein SEQ ID NO:196 is a clone designated herein as "DNA57690-1374".

Figure 125 shows the amino acid sequence (SEQ ID NO:197) derived from the coding sequence of SEQ ID NO:196 shown in Figure 124.

Figure 126 shows a nucleotide sequence (SEQ ID NO:198) of a native sequence PRO1056 (UNQ521) cDNA, wherein SEQ ID NO:198 is a clone designated herein as "DNA57693-1424".

Figure 127 shows the amino acid sequence (SEQ ID NO:199) derived from the coding sequence of SEQ ID NO:198 shown in Figure 126.

Figure 128 shows a nucleotide sequence (SEQ ID NO:200) of a native sequence PRO826 (UNQ467) cDNA, wherein SEQ ID NO:200 is a clone designated herein as "DNA57694-1341".

Figure 129 shows the amino acid sequence (SEQ ID NO:201) derived from the coding sequence of SEQ ID NO:200 shown in Figure 128.

Figure 130 shows a nucleotide sequence (SEQ ID NO:202) of a native sequence PRO819 (UNQ466) cDNA, wherein SEQ ID NO:202 is a clone designated herein as "DNA57695-1340".

Figure 131 shows the amino acid sequence (SEQ ID NO:203) derived from the coding sequence of SEQ ID NO:202 shown in Figure 130.

Figure 132 shows a nucleotide sequence (SEQ ID NO:204) of a native sequence PRO1006 (UNQ490) cDNA, wherein SEQ ID NO:204 is a clone designated herein as "DNA57699-1412".

Figure 133 shows the amino acid sequence (SEQ ID NO:205) derived from the coding sequence of SEQ ID NO:204 shown in Figure 132.

Figure 134 shows a nucleotide sequence (SEQ ID NO:206) of a native sequence PRO1112 (UNQ555) cDNA, wherein SEQ ID NO:206 is a clone designated herein as "DNA57702-1476".

Figure 135 shows the amino acid sequence (SEQ ID NO:207) derived from the coding sequence of SEQ ID NO:206 shown in Figure 134.

5 Figure 136 shows a nucleotide sequence (SEQ ID NO:208) of a native sequence PRO1074 (UNQ531) cDNA, wherein SEQ ID NO:208 is a clone designated herein as "DNA57704-1452".

Figure 137 shows the amino acid sequence (SEQ ID NO:209) derived from the coding sequence of SEQ ID NO:208 shown in Figure 136.

Figure 138 shows a nucleotide sequence (SEQ ID NO:210) of a native sequence PRO1005 (UNQ489) cDNA, wherein SEQ ID NO:210 is a clone designated herein as "DNA57708-1005".

10 Figure 139 shows the amino acid sequence (SEQ ID NO:211) derived from the coding sequence of SEQ ID NO:210 shown in Figure 138.

Figure 140 shows a nucleotide sequence (SEQ ID NO:212) of a native sequence PRO1073 (UNQ530) cDNA, wherein SEQ ID NO:212 is a clone designated herein as "DNA57710-1451".

15 Figure 141 shows the amino acid sequence (SEQ ID NO:213) derived from the coding sequence of SEQ ID NO:212 shown in Figure 140.

Figure 142 shows a nucleotide sequence designated herein as DNA55938 (SEQ ID NO:214).

Figure 143 shows a nucleotide sequence (SEQ ID NO:215) of a native sequence PRO1152 (UNQ582) cDNA, wherein SEQ ID NO:215 is a clone designated herein as "DNA57711-1501".

20 Figure 144 shows the amino acid sequence (SEQ ID NO:216) derived from the coding sequence of SEQ ID NO:215 shown in Figure 143.

Figure 145 shows a nucleotide sequence designated herein as DNA55807 (SEQ ID NO:217).

Figure 146 shows a nucleotide sequence (SEQ ID NO:218) of a native sequence PRO1136 (UNQ574) cDNA, wherein SEQ ID NO:218 is a clone designated herein as "DNA57827-1493".

25 Figure 147 shows the amino acid sequence (SEQ ID NO:219) derived from the coding sequence of SEQ ID NO:218 shown in Figure 146.

Figure 148 shows a nucleotide sequence (SEQ ID NO:220) of a native sequence PRO813 (UNQ465) cDNA, wherein SEQ ID NO:220 is a clone designated herein as "DNA57834-1339".

Figure 149 shows the amino acid sequence (SEQ ID NO:221) derived from the coding sequence of SEQ ID NO:220 shown in Figure 148.

30 Figure 150 shows a nucleotide sequence (SEQ ID NO:222) of a native sequence PRO809 (UNQ464) cDNA, wherein SEQ ID NO:222 is a clone designated herein as "DNA57836-1338".

Figure 151 shows the amino acid sequence (SEQ ID NO:223) derived from the coding sequence of SEQ ID NO:222 shown in Figure 150.

35 Figure 152 shows a nucleotide sequence (SEQ ID NO:224) of a native sequence PRO791 (UNQ463) cDNA, wherein SEQ ID NO:224 is a clone designated herein as "DNA57838-1337".

Figure 153 shows the amino acid sequence (SEQ ID NO:225) derived from the coding sequence of SEQ ID NO:224 shown in Figure 152.

Figure 154 shows a nucleotide sequence (SEQ ID NO:226) of a native sequence PRO1004 (UNQ488) cDNA, wherein SEQ ID NO:226 is a clone designated herein as "DNA57844-1410".

Figure 155 shows the amino acid sequence (SEQ ID NO:227) derived from the coding sequence of SEQ ID NO:226 shown in Figure 154.

5 Figure 156 shows a nucleotide sequence (SEQ ID NO:228) of a native sequence PRO1111 (UNQ554) cDNA, wherein SEQ ID NO:228 is a clone designated herein as "DNA58721-1475".

Figure 157 shows the amino acid sequence (SEQ ID NO:229) derived from the coding sequence of SEQ ID NO:228 shown in Figure 156.

Figure 158 shows a nucleotide sequence (SEQ ID NO:230) of a native sequence PRO1344 (UNQ699) cDNA, wherein SEQ ID NO:230 is a clone designated herein as "DNA58723-1588".

10 Figure 159 shows the amino acid sequence (SEQ ID NO:231) derived from the coding sequence of SEQ ID NO:230 shown in Figure 158.

Figure 160 shows a nucleotide sequence (SEQ ID NO:235) of a native sequence PRO1109 (UNQ552) cDNA, wherein SEQ ID NO:235 is a clone designated herein as "DNA58737-1473".

15 Figure 161 shows the amino acid sequence (SEQ ID NO:236) derived from the coding sequence of SEQ ID NO:235 shown in Figure 160.

Figure 162 shows a nucleotide sequence (SEQ ID NO:240) of a native sequence PRO1383 (UNQ719) cDNA, wherein SEQ ID NO:240 is a clone designated herein as "DNA58743-1609".

Figure 163 shows the amino acid sequence (SEQ ID NO:241) derived from the coding sequence of SEQ ID NO:240 shown in Figure 162.

20 Figure 164 shows a nucleotide sequence (SEQ ID NO:245) of a native sequence PRO1003 (UNQ487) cDNA, wherein SEQ ID NO:245 is a clone designated herein as "DNA58846-1409".

Figure 165 shows the amino acid sequence (SEQ ID NO:246) derived from the coding sequence of SEQ ID NO:245 shown in Figure 164.

25 Figure 166 shows a nucleotide sequence (SEQ ID NO:247) of a native sequence PRO1108 (UNQ551) cDNA, wherein SEQ ID NO:247 is a clone designated herein as "DNA58848-1472".

Figure 167 shows the amino acid sequence (SEQ ID NO:248) derived from the coding sequence of SEQ ID NO:247 shown in Figure 166.

Figure 168 shows a nucleotide sequence (SEQ ID NO:249) of a native sequence PRO1137 (UNQ575) cDNA, wherein SEQ ID NO:249 is a clone designated herein as "DNA58849-1494".

30 Figure 169 shows the amino acid sequence (SEQ ID NO:250) derived from the coding sequence of SEQ ID NO:249 shown in Figure 168.

Figure 170 shows a nucleotide sequence (SEQ ID NO:252) of a native sequence PRO1138 (UNQ576) cDNA, wherein SEQ ID NO:252 is a clone designated herein as "DNA58850-1495".

35 Figure 171 shows the amino acid sequence (SEQ ID NO:253) derived from the coding sequence of SEQ ID NO:252 shown in Figure 170.

Figure 172 shows a nucleotide sequence designated herein as DNA49140 (SEQ ID NO:254).



Figure 173 shows a nucleotide sequence (SEQ ID NO:255) of a native sequence PRO1054 (UNQ519) cDNA, wherein SEQ ID NO:255 is a clone designated herein as "DNA58853-1423".

Figure 174 shows the amino acid sequence (SEQ ID NO:256) derived from the coding sequence of SEQ ID NO:255 shown in Figure 173.

5 Figure 175 shows a nucleotide sequence (SEQ ID NO:257) of a native sequence PRO994 (UNQ518) cDNA, wherein SEQ ID NO:257 is a clone designated herein as "DNA58855-1422".

Figure 176 shows the amino acid sequence (SEQ ID NO:258) derived from the coding sequence of SEQ ID NO:257 shown in Figure 175.

Figure 177 shows a nucleotide sequence (SEQ ID NO:259) of a native sequence PRO812 (UNQ517) cDNA, wherein SEQ ID NO:259 is a clone designated herein as "DNA59205-1421".

10 Figure 178 shows the amino acid sequence (SEQ ID NO:260) derived from the coding sequence of SEQ ID NO:259 shown in Figure 177.

Figure 179 shows a nucleotide sequence (SEQ ID NO:261) of a native sequence PRO1069 (UNQ526) cDNA, wherein SEQ ID NO:261 is a clone designated herein as "DNA59211-1450".

15 Figure 180 shows the amino acid sequence (SEQ ID NO:262) derived from the coding sequence of SEQ ID NO:261 shown in Figure 179.

Figure 181 shows a nucleotide sequence (SEQ ID NO:263) of a native sequence PRO1129 (UNQ568) cDNA, wherein SEQ ID NO:263 is a clone designated herein as "DNA59213-1487".

Figure 182 shows the amino acid sequence (SEQ ID NO:264) derived from the coding sequence of SEQ ID NO:263 shown in Figure 181.

20 Figure 183 shows a nucleotide sequence (SEQ ID NO:265) of a native sequence PRO1068 (UNQ525) cDNA, wherein SEQ ID NO:265 is a clone designated herein as "DNA59214-1449".

Figure 184 shows the amino acid sequence (SEQ ID NO:266) derived from the coding sequence of SEQ ID NO:265 shown in Figure 183.

25 Figure 185 shows a nucleotide sequence (SEQ ID NO:267) of a native sequence PRO1066 (UNQ524) cDNA, wherein SEQ ID NO:267 is a clone designated herein as "DNA59215-1425".

Figure 186 shows the amino acid sequence (SEQ ID NO:268) derived from the coding sequence of SEQ ID NO:267 shown in Figure 185.

Figure 187 shows a nucleotide sequence (SEQ ID NO:269) of a native sequence PRO1184 (UNQ598) cDNA, wherein SEQ ID NO:269 is a clone designated herein as "DNA59220-1514".

30 Figure 188 shows the amino acid sequence (SEQ ID NO:270) derived from the coding sequence of SEQ ID NO:269 shown in Figure 187.

Figure 189 shows a nucleotide sequence (SEQ ID NO:271) of a native sequence PRO1360 (UNQ709) cDNA, wherein SEQ ID NO:271 is a clone designated herein as "DNA59488-1603".

35 Figure 190 shows the amino acid sequence (SEQ ID NO:272) derived from the coding sequence of SEQ ID NO:271 shown in Figure 189.

Figure 191 shows a nucleotide sequence (SEQ ID NO:273) of a native sequence PRO1029 (UNQ514) cDNA, wherein SEQ ID NO:273 is a clone designated herein as "DNA59493-1420".

Figure 192 shows the amino acid sequence (SEQ ID NO:274) derived from the coding sequence of SEQ ID NO:273 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO:275) of a native sequence PRO1139 (UNQ577) cDNA, wherein SEQ ID NO:275 is a clone designated herein as "DNA59497-1496".

5 Figure 194 shows the amino acid sequence (SEQ ID NO:276) derived from the coding sequence of SEQ ID NO:275 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:277) of a native sequence PRO1309 (UNQ675) cDNA, wherein SEQ ID NO:277 is a clone designated herein as "DNA59588-1571".

Figure 196 shows the amino acid sequence (SEQ ID NO:278) derived from the coding sequence of SEQ ID NO:277 shown in Figure 195.

10 Figure 197 shows a nucleotide sequence (SEQ ID NO:280) of a native sequence PRO1028 (UNQ513) cDNA, wherein SEQ ID NO:280 is a clone designated herein as "DNA59603-1419".

Figure 198 shows the amino acid sequence (SEQ ID NO:281) derived from the coding sequence of SEQ ID NO:280 shown in Figure 197.

15 Figure 199 shows a nucleotide sequence (SEQ ID NO:282) of a native sequence PRO1027 (UNQ512) cDNA, wherein SEQ ID NO:282 is a clone designated herein as "DNA59605-1418".

Figure 200 shows the amino acid sequence (SEQ ID NO:283) derived from the coding sequence of SEQ ID NO:282 shown in Figure 199.

Figure 201 shows a nucleotide sequence (SEQ ID NO:284) of a native sequence PRO1107 (UNQ550) cDNA, wherein SEQ ID NO:284 is a clone designated herein as "DNA59606-1471".

20 Figure 202 shows the amino acid sequence (SEQ ID NO:285) derived from the coding sequence of SEQ ID NO:284 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:286) of a native sequence PRO1140 (UNQ578) cDNA, wherein SEQ ID NO:286 is a clone designated herein as "DNA59607-1497".

25 Figure 204 shows the amino acid sequence (SEQ ID NO:287) derived from the coding sequence of SEQ ID NO:286 shown in Figure 203.

Figure 205 shows a nucleotide sequence (SEQ ID NO:288) of a native sequence PRO1106 (UNQ549) cDNA, wherein SEQ ID NO:288 is a clone designated herein as "DNA59609-1470".

Figure 206 shows the amino acid sequence (SEQ ID NO:289) derived from the coding sequence of SEQ ID NO:288 shown in Figure 205.

30 Figure 207 shows a nucleotide sequence (SEQ ID NO:290) of a native sequence PRO1291 (UNQ659) cDNA, wherein SEQ ID NO:290 is a clone designated herein as "DNA59610-1556".

Figure 208 shows the amino acid sequence (SEQ ID NO:291) derived from the coding sequence of SEQ ID NO:290 shown in Figure 207.

35 Figure 209 shows a nucleotide sequence (SEQ ID NO:292) of a native sequence PRO1105 (UNQ548) cDNA, wherein SEQ ID NO:292 is a clone designated herein as "DNA59612-1466".

Figure 210 shows the amino acid sequence (SEQ ID NO:293) derived from the coding sequence of SEQ ID NO:292 shown in Figure 209.

Figure 211 shows a nucleotide sequence (SEQ ID NO:294) of a native sequence PRO511 (UNQ511) cDNA, wherein SEQ ID NO:294 is a clone designated herein as "DNA59613-1417".

Figure 212 shows the amino acid sequence (SEQ ID NO:295) derived from the coding sequence of SEQ ID NO:294 shown in Figure 211.

5 Figure 213 shows a nucleotide sequence (SEQ ID NO:296) of a native sequence PRO1104 (UNQ547) cDNA, wherein SEQ ID NO:296 is a clone designated herein as "DNA59616-1465".

Figure 214 shows the amino acid sequence (SEQ ID NO:297) derived from the coding sequence of SEQ ID NO:296 shown in Figure 213.

Figure 215 shows a nucleotide sequence (SEQ ID NO:298) of a native sequence PRO1100 (UNQ546) cDNA, wherein SEQ ID NO:298 is a clone designated herein as "DNA59619-1464".

10 Figure 216 shows the amino acid sequence (SEQ ID NO:299) derived from the coding sequence of SEQ ID NO:298 shown in Figure 215.

Figure 217 shows a nucleotide sequence (SEQ ID NO:300) of a native sequence PRO836 (UNQ545) cDNA, wherein SEQ ID NO:300 is a clone designated herein as "DNA59620-1463".

15 Figure 218 shows the amino acid sequence (SEQ ID NO:301) derived from the coding sequence of SEQ ID NO:300 shown in Figure 217.

Figure 219 shows a nucleotide sequence (SEQ ID NO:302) of a native sequence PRO1141 (UNQ579) cDNA, wherein SEQ ID NO:302 is a clone designated herein as "DNA59625-1498".

Figure 220 shows the amino acid sequence (SEQ ID NO:303) derived from the coding sequence of SEQ ID NO:302 shown in Figure 219.

20 Figure 221 shows a nucleotide sequence designated herein as DNA33128 (SEQ ID NO:304).

Figure 222 shows a nucleotide sequence designated herein as DNA34256 (SEQ ID NO:305).

Figure 223 shows a nucleotide sequence designated herein as DNA47941 (SEQ ID NO:306).

Figure 224 shows a nucleotide sequence designated herein as DNA54389 (SEQ ID NO:307).

25 Figure 225 shows a nucleotide sequence (SEQ ID NO:308) of a native sequence PRO1132 (UNQ570) cDNA, wherein SEQ ID NO:308 is a clone designated herein as "DNA59767-1489".

Figure 226 shows the amino acid sequence (SEQ ID NO:309) derived from the coding sequence of SEQ ID NO:308 shown in Figure 225.

Figure 227 shows a nucleotide sequence (SEQ ID NO:313) of a native sequence PRO1346 cDNA, wherein SEQ ID NO:313 is a clone designated herein as "DNA59776-1600".

30 Figure 228 shows the amino acid sequence (SEQ ID NO:314) derived from the coding sequence of SEQ ID NO:313 shown in Figure 227.

Figure 229 shows a nucleotide sequence (SEQ ID NO:318) of a native sequence PRO1131 (UNQ569) cDNA, wherein SEQ ID NO:318 is a clone designated herein as "DNA59777-1480".

35 Figure 230 shows the amino acid sequence (SEQ ID NO:319) derived from the coding sequence of SEQ ID NO:318 shown in Figure 229.

Figure 231 shows a nucleotide sequence designated herein as DNA43546 (SEQ ID NO:320).

Figure 232 shows a nucleotide sequence (SEQ ID NO:325) of a native sequence PRO1281 (UNQ651) cDNA, wherein SEQ ID NO:325 is a clone designated herein as "DNA59820-1549".

Figure 233 shows the amino acid sequence (SEQ ID NO:326) derived from the coding sequence of SEQ ID NO:325 shown in Figure 232.

Figure 234 shows a nucleotide sequence (SEQ ID NO:333) of a native sequence PRO1064 (UNQ111) cDNA, wherein SEQ ID NO:333 is a clone designated herein as "DNA59827-1426".

Figure 235 shows the amino acid sequence (SEQ ID NO:334) derived from the coding sequence of SEQ ID NO:333 shown in Figure 234.

Figure 236 shows a nucleotide sequence designated herein as DNA45288 (SEQ ID NO:335).

Figure 237 shows a nucleotide sequence (SEQ ID NO:339) of a native sequence PRO1379 (UNQ716) cDNA, wherein SEQ ID NO:339 is a clone designated herein as "DNA59828-1608".

Figure 238 shows the amino acid sequence (SEQ ID NO:340) derived from the coding sequence of SEQ ID NO:339 shown in Figure 237.

Figure 239 shows a nucleotide sequence (SEQ ID NO:344) of a native sequence PRO844 (UNQ544) cDNA, wherein SEQ ID NO:344 is a clone designated herein as "DNA59838-1462".

Figure 240 shows the amino acid sequence (SEQ ID NO:345) derived from the coding sequence of SEQ ID NO:344 shown in Figure 239.

Figure 241 shows a nucleotide sequence (SEQ ID NO:346) of a native sequence PRO848 (UNQ543) cDNA, wherein SEQ ID NO:346 is a clone designated herein as "DNA59839-1461".

Figure 242 shows the amino acid sequence (SEQ ID NO:347) derived from the coding sequence of SEQ ID NO:346 shown in Figure 241.

Figure 243 shows a nucleotide sequence (SEQ ID NO:348) of a native sequence PRO1097 (UNQ542) cDNA, wherein SEQ ID NO:348 is a clone designated herein as "DNA59841-1460".

Figure 244 shows the amino acid sequence (SEQ ID NO:349) derived from the coding sequence of SEQ ID NO:348 shown in Figure 243.

Figure 245 shows a nucleotide sequence (SEQ ID NO:350) of a native sequence PRO1153 (UNQ583) cDNA, wherein SEQ ID NO:350 is a clone designated herein as "DNA59842-1502".

Figure 246 shows the amino acid sequence (SEQ ID NO:351) derived from the coding sequence of SEQ ID NO:350 shown in Figure 245.

Figure 247 shows a nucleotide sequence (SEQ ID NO:352) of a native sequence PRO1154 (UNQ584) cDNA, wherein SEQ ID NO:352 is a clone designated herein as "DNA59846-1503".

Figure 248 shows the amino acid sequence (SEQ ID NO:353) derived from the coding sequence of SEQ ID NO:352 shown in Figure 247.

Figure 249 shows a nucleotide sequence (SEQ ID NO:354) of a native sequence PRO1181 (UNQ595) cDNA, wherein SEQ ID NO:354 is a clone designated herein as "DNA59847-1511".

Figure 250 shows the amino acid sequence (SEQ ID NO:355) derived from the coding sequence of SEQ ID NO:354 shown in Figure 249.



Figure 251 shows a nucleotide sequence (SEQ ID NO:356) of a native sequence PRO1182 (UNQ596) cDNA, wherein SEQ ID NO:356 is a clone designated herein as "DNA59848-1512".

Figure 252 shows the amino acid sequence (SEQ ID NO:357) derived from the coding sequence of SEQ ID NO:356 shown in Figure 251.

Figure 253 shows a nucleotide sequence (SEQ ID NO:358) of a native sequence PRO1155 (UNQ585) cDNA, wherein SEQ ID NO:358 is a clone designated herein as "DNA59849-1504".

Figure 254 shows the amino acid sequence (SEQ ID NO:359) derived from the coding sequence of SEQ ID NO:358 shown in Figure 253.

Figure 255 shows a nucleotide sequence (SEQ ID NO:360) of a native sequence PRO1156 (UNQ586) cDNA, wherein SEQ ID NO:360 is a clone designated herein as "DNA59853-1505".

Figure 256 shows the amino acid sequence (SEQ ID NO:361) derived from the coding sequence of SEQ ID NO:360 shown in Figure 255.

Figure 257 shows a nucleotide sequence (SEQ ID NO:362) of a native sequence PRO1098 (UNQ541) cDNA, wherein SEQ ID NO:362 is a clone designated herein as "DNA59854-1459".

Figure 258 shows the amino acid sequence (SEQ ID NO:363) derived from the coding sequence of SEQ ID NO:362 shown in Figure 257.

Figure 259 shows a nucleotide sequence (SEQ ID NO:364) of a native sequence PRO1127 (UNQ565) cDNA, wherein SEQ ID NO:364 is a clone designated herein as "DNA60283-1484".

Figure 260 shows the amino acid sequence (SEQ ID NO:365) derived from the coding sequence of SEQ ID NO:364 shown in Figure 259.

Figure 261 shows a nucleotide sequence (SEQ ID NO:366) of a native sequence PRO1126 (UNQ564) cDNA, wherein SEQ ID NO:366 is a clone designated herein as "DNA60615-1483".

Figure 262 shows the amino acid sequence (SEQ ID NO:367) derived from the coding sequence of SEQ ID NO:366 shown in Figure 261.

Figure 263 shows a nucleotide sequence (SEQ ID NO:368) of a native sequence PRO1125 (UNQ563) cDNA, wherein SEQ ID NO:368 is a clone designated herein as "DNA60619-1482".

Figure 264 shows the amino acid sequence (SEQ ID NO:369) derived from the coding sequence of SEQ ID NO:368 shown in Figure 263.

Figure 265 shows a nucleotide sequence (SEQ ID NO:370) of a native sequence PRO1186 (UNQ600) cDNA, wherein SEQ ID NO:370 is a clone designated herein as "DNA60621-1516".

Figure 266 shows the amino acid sequence (SEQ ID NO:371) derived from the coding sequence of SEQ ID NO:370 shown in Figure 265.

Figure 267 shows a nucleotide sequence (SEQ ID NO:372) of a native sequence PRO1198 (UNQ611) cDNA, wherein SEQ ID NO:372 is a clone designated herein as "DNA60622-1525".

Figure 268 shows the amino acid sequence (SEQ ID NO:373) derived from the coding sequence of SEQ ID NO:372 shown in Figure 267.

Figure 269 shows a nucleotide sequence (SEQ ID NO:374) of a native sequence PRO1158 (UNQ588) cDNA, wherein SEQ ID NO:374 is a clone designated herein as "DNA60625-1507".

Figure 270 shows the amino acid sequence (SEQ ID NO:375) derived from the coding sequence of SEQ ID NO:374 shown in Figure 269.

Figure 271 shows a nucleotide sequence (SEQ ID NO:376) of a native sequence PRO1159 (UNQ589) cDNA, wherein SEQ ID NO:376 is a clone designated herein as "DNA60627-1508".

5 Figure 272 shows the amino acid sequence (SEQ ID NO:377) derived from the coding sequence of SEQ ID NO:376 shown in Figure 271.

Figure 273 shows a nucleotide sequence (SEQ ID NO:378) of a native sequence PRO1124 (UNQ562) cDNA, wherein SEQ ID NO:378 is a clone designated herein as "DNA60629-1481".

Figure 274 shows the amino acid sequence (SEQ ID NO:379) derived from the coding sequence of SEQ ID NO:378 shown in Figure 273.

10 Figure 275 shows a nucleotide sequence (SEQ ID NO:380) of a native sequence PRO1287 (UNQ656) cDNA, wherein SEQ ID NO:380 is a clone designated herein as "DNA61755-1554".

Figure 276 shows the amino acid sequence (SEQ ID NO:381) derived from the coding sequence of SEQ ID NO:380 shown in Figure 275.

15 Figure 277 shows a nucleotide sequence (SEQ ID NO:386) of a native sequence PRO1312 (UNQ678) cDNA, wherein SEQ ID NO:386 is a clone designated herein as "DNA61873-1574".

Figure 278 shows the amino acid sequence (SEQ ID NO:387) derived from the coding sequence of SEQ ID NO:386 shown in Figure 277.

Figure 279 shows a nucleotide sequence (SEQ ID NO:388) of a native sequence PRO1192 (UNQ606) cDNA, wherein SEQ ID NO:388 is a clone designated herein as "DNA62814-1521".

20 Figure 280 shows the amino acid sequence (SEQ ID NO:389) derived from the coding sequence of SEQ ID NO:388 shown in Figure 279.

Figure 281 shows a nucleotide sequence (SEQ ID NO:393) of a native sequence PRO1160 (UNQ590) cDNA, wherein SEQ ID NO:393 is a clone designated herein as "DNA62872-1509".

25 Figure 282 shows the amino acid sequence (SEQ ID NO:394) derived from the coding sequence of SEQ ID NO:393 shown in Figure 281.

Figure 283 shows a nucleotide sequence (SEQ ID NO:398) of a native sequence PRO1187 (UNQ601) cDNA, wherein SEQ ID NO:398 is a clone designated herein as "DNA62876-1517".

Figure 284 shows the amino acid sequence (SEQ ID NO:399) derived from the coding sequence of SEQ ID NO:398 shown in Figure 283.

30 Figure 285 shows a nucleotide sequence (SEQ ID NO:400) of a native sequence PRO1185 (UNQ599) cDNA, wherein SEQ ID NO:400 is a clone designated herein as "DNA62881-1515".

Figure 286 shows the amino acid sequence (SEQ ID NO:401) derived from the coding sequence of SEQ ID NO:400 shown in Figure 285.

35 Figure 287 shows a nucleotide sequence (SEQ ID NO:402) of a native sequence PRO1345 (UNQ700) cDNA, wherein SEQ ID NO:402 is a clone designated herein as "DNA64852-1589".

Figure 288 shows the amino acid sequence (SEQ ID NO:403) derived from the coding sequence of SEQ ID NO:402 shown in Figure 287.

Figure 289 shows a nucleotide sequence (SEQ ID NO:407) of a native sequence PRO1245 (UNQ629) cDNA, wherein SEQ ID NO:407 is a clone designated herein as "DNA64884-1527".

Figure 290 shows the amino acid sequence (SEQ ID NO:408) derived from the coding sequence of SEQ ID NO:407 shown in Figure 289.

5 Figure 291 shows a nucleotide sequence (SEQ ID NO:409) of a native sequence PRO1358 (UNQ707) cDNA, wherein SEQ ID NO:409 is a clone designated herein as "DNA64890-1612".

Figure 292 shows the amino acid sequence (SEQ ID NO:410) derived from the coding sequence of SEQ ID NO:409 shown in Figure 291.

Figure 293 shows a nucleotide sequence (SEQ ID NO:411) of a native sequence PRO1195 (UNQ608) cDNA, wherein SEQ ID NO:411 is a clone designated herein as "DNA65412-1523".

10 Figure 294 shows the amino acid sequence (SEQ ID NO:412) derived from the coding sequence of SEQ ID NO:411 shown in Figure 293.

Figure 295 shows a nucleotide sequence (SEQ ID NO:413) of a native sequence PRO1270 (UNQ640) cDNA, wherein SEQ ID NO:413 is a clone designated herein as "DNA66308-1537".

15 Figure 296 shows the amino acid sequence (SEQ ID NO:414) derived from the coding sequence of SEQ ID NO:413 shown in Figure 295.

Figure 297 shows a nucleotide sequence (SEQ ID NO:415) of a native sequence PRO1271 (UNQ641) cDNA, wherein SEQ ID NO:415 is a clone designated herein as "DNA66309-1538".

Figure 298 shows the amino acid sequence (SEQ ID NO:416) derived from the coding sequence of SEQ ID NO:415 shown in Figure 297.

20 Figure 299 shows a nucleotide sequence (SEQ ID NO:417) of a native sequence PRO1375 (UNQ712) cDNA, wherein SEQ ID NO:417 is a clone designated herein as "DNA67004-1614".

Figure 300 shows the amino acid sequence (SEQ ID NO:418) derived from the coding sequence of SEQ ID NO:417 shown in Figure 299.

25 Figure 301 shows a nucleotide sequence (SEQ ID NO:419) of a native sequence PRO1385 (UNQ720) cDNA, wherein SEQ ID NO:419 is a clone designated herein as "DNA68869-1610".

Figure 302 shows the amino acid sequence (SEQ ID NO:420) derived from the coding sequence of SEQ ID NO:419 shown in Figure 301.

Figure 303 shows a nucleotide sequence (SEQ ID NO:421) of a native sequence PRO1387 (UNQ722) cDNA, wherein SEQ ID NO:421 is a clone designated herein as "DNA68872-1620".

30 Figure 304 shows the amino acid sequence (SEQ ID NO:422) derived from the coding sequence of SEQ ID NO:421 shown in Figure 303.

Figure 305 shows a nucleotide sequence (SEQ ID NO:423) of a native sequence PRO1384 (UNQ721) cDNA, wherein SEQ ID NO:423 is a clone designated herein as "DNA71159-1617".

35 Figure 306 shows the amino acid sequence (SEQ ID NO:424) derived from the coding sequence of SEQ ID NO:423 shown in Figure 305.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTSI. Definitions

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i.e., PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO281 polypeptide is a mature or full-length native sequence PRO281 polypeptide comprising amino acids 1 to 345 of Figure 2 (SEQ ID NO:2), the native sequence PRO276 is a full-length or mature native sequence PRO276 comprising amino acids 1 through 251 of Figure 4 (SEQ ID NO:6), the native sequence PRO189 is a full-length or mature native sequence PRO189 comprising amino acids 1 through 367 of Figure 6 (SEQ ID NO:8), the native sequence PRO190 polypeptide is a full-length or mature native sequence PRO190 polypeptide comprising amino acids 1 through 424 of Figure 9 (SEQ ID NO:14), the native sequence PRO341 is a mature or full-length native sequence PRO341 comprising amino acids 1 to 458 of Figure 12 (SEQ ID NO:20), the native sequence PRO180 is a full-length or mature native sequence PRO180 comprising amino acids 1 through 266 of Figure 15 (SEQ ID NO:23), the native sequence PRO194 polypeptide is a mature or full-length native sequence PRO194 polypeptide comprising amino acids 1 to 264 of Figure 18 (SEQ ID NO:28), the native sequence PRO203 polypeptide is a mature or full-length native sequence PRO203 polypeptide comprising amino acids 1 to 347 of Figure 20 (SEQ ID NO:30), the native sequence PRO290 is a full-length or mature native sequence PRO290 comprising amino acids 1 through 1003 of Figure 23 (SEQ ID NO:33), the native sequence PRO874 polypeptide comprises amino acids 1 to 321 of Figure 25 (SEQ ID NO:36), the native sequence PRO710 polypeptide is a mature or full-length native sequence PRO710 polypeptide comprising amino acids 1 to 566 of Figure 27 (SEQ ID NO:41), the native sequence PRO1151 is a mature or full-length native sequence PRO1151 comprising amino acids 1 to 259 of Figure 30 (SEQ ID NO:47), the native sequence PRO1282 is a full-length or mature native sequence PRO1282 comprising amino acids 1 or about 24 through 673 of Figure 32 (SEQ ID NO:52), the native sequence PRO358 is a mature or full-length native sequence PRO358 polypeptide comprising amino acids 1 to 811 of Figure 34 (SEQ ID NO:57), the native sequence PRO1310 is a full-length or mature native sequence PRO1310 comprising amino acids 1 through 765 of Figure 36 (SEQ ID NO:62), the native sequence PRO698 polypeptide is a mature or full-length native sequence PRO698 polypeptide comprising amino acids 1 to 510 of Figure 38 (SEQ ID NO:67), the native



sequence PRO732 polypeptide is a mature or full-length native sequence PRO732 polypeptide comprising amino acids 1 to 453 of Figure 41 (SEQ ID NO:73), the native sequence PRO1120 is a full-length or mature native sequence PRO1120 comprising amino acids 1 or about 18 to 867 of Figure 47 (SEQ ID NO:84), the native sequence PRO537 is a mature or full-length native sequence PRO537 comprising amino acids 1 to 115 of Figure 49 (SEQ ID NO:95), the native sequence PRO536 is a mature or full-length native sequence PRO536 comprising amino acids 1 to 313 of Figure 51 (SEQ ID NO:97), the native sequence PRO535 is a mature or full-length native sequence PRO535 comprising amino acids 1 to 201 of Figure 53 (SEQ ID NO:99), the native sequence PRO718 polypeptide is a mature or full-length native sequence PRO718 polypeptide comprising amino acids 1 to 157 of Figure 57 (SEQ ID NO:103), the native sequence PRO872 polypeptide is a mature or full-length native sequence PRO872 polypeptide comprising amino acids 1 to 610 of Figure 64 (SEQ ID NO:113), the native sequence PRO1063 polypeptide is a mature or full-length native sequence PRO1063 polypeptide comprising amino acids 1 to 301 of Figure 66 (SEQ ID NO:115), the native sequence PRO619 is a full-length or mature native sequence PRO619 comprising amino acids 1 or about 21 through 123 of Figure 68 (SEQ ID NO:117), the native sequence PRO943 is a mature or full-length native sequence PRO943 comprising amino acids 1 to 504 of Figure 70 (SEQ ID NO:119), the native sequence PRO1188 is a full-length or mature native sequence PRO1188 comprising amino acids 1 or about 22 to 1184 of Figure 72 (SEQ ID NO:124), the native sequence PRO1133 is a full-length or mature native sequence PRO1133 comprising amino acids 1 or about 19 through 438 of Figure 74 (SEQ ID NO:129), the native sequence PRO784 is a mature or full-length native sequence PRO784 comprising amino acids 16 to 228 of Figure 76 (SEQ ID NO:135), the native sequence PRO783 polypeptide is a mature or full-length native sequence PRO783 polypeptide comprising amino acids 1 to 489 of Figure 79 (SEQ ID NO:138), the native sequence PRO820 is a full-length or mature native sequence PRO820 comprising amino acids 1 or 16 through 124 of Figure 83 (SEQ ID NO:146), the native sequence PRO1080 is a full-length or mature native sequence PRO1080 comprising amino acids 1 or 23 through 358 of Figure 85 (SEQ ID NO:148), the native sequence PRO1079 is a full-length or mature native sequence PRO1079 comprising amino acids 1 or about 30 to 226 of Figure 88 (SEQ ID NO:151), the native sequence PRO793 is a mature or full-length native sequence PRO793 comprising amino acids 1 to 138 of Figure 90 (SEQ ID NO:153), the native sequence PRO1016 is a full-length or mature native sequence PRO1016 comprising amino acids 1 or 19 through 378 of Figure 93 (SEQ ID NO:156), the native sequence PRO1013 polypeptide is a full-length or mature native sequence PRO1013 polypeptide comprising amino acids 1 or 20 through 409 of Figure 95 (SEQ ID NO:158), the native sequence PRO937 polypeptide is a mature or full-length native sequence PRO937 polypeptide comprising amino acids 1 to 556 of Figure 97 (SEQ ID NO:160), the native sequence PRO842 is a full-length or mature native sequence PRO842 comprising amino acids 1 or about 23 to 119 of Figure 99 (SEQ ID NO:165), the native sequence PRO839 is a full-length or mature native sequence PRO839 comprising amino acids 1 or about 24 to 87 of Figure 101 (SEQ ID NO:167), the native sequence PRO1180 polypeptide is a mature or full-length native sequence PRO1180 polypeptide comprising amino acids 1 to 277 of Figure 103 (SEQ ID NO:169), the native sequence PRO1134 is a mature or full-length native sequence PRO1134 comprising amino acids 1 to 371 of Figure 105 (SEQ ID NO:171), the native sequence PRO830 is a mature or full-length native sequence PRO830 comprising amino acids 1 to 87 of Figure 109 (SEQ ID NO:175), the native sequence

PRO1115 is a full-length or mature native sequence PRO1115 comprising amino acids 1 or about 21 to 445 of Figure 111 (SEQ ID NO:177), the native sequence PRO1277 is a full-length or mature native sequence PRO1277 comprising amino acids 1 or about 27 to 678 of Figure 113 (SEQ ID NO:179), the native sequence PRO1135 polypeptide is a mature or full-length native sequence PRO1135 polypeptide comprising amino acids 1 to 541 of Figure 115 (SEQ ID NO:181), the native sequence PRO1114 interferon receptor is a mature or full-length native sequence PRO1114 interferon receptor comprising amino acids 1 to 311 of Figure 118 (SEQ ID NO:184), the native sequence PRO828 polypeptide is a mature or full-length native sequence PRO828 polypeptide comprising amino acids 1 to 187 of Figure 120 (SEQ ID NO:189), the native sequence PRO1009 is a full-length or mature native sequence PRO1009 comprising amino acids 1 or 23 to 615 of Figure 122 (SEQ ID NO:194), the native sequence PRO1007 polypeptide is a full-length or mature native sequence PRO1007 polypeptide comprising amino acids 1 or 31 through 346 of Figure 125 (SEQ ID NO:197), the native sequence PRO1056 is a mature or full-length native sequence PRO1056 comprising amino acids 1 to 120 of Figure 127 (SEQ ID NO:199), the native sequence PRO826 is a mature or full-length native sequence PRO826 comprising amino acids 1 to 99 of Figure 129 (SEQ ID NO:201), the native sequence PRO819 is a mature or full-length native sequence PRO819 comprising amino acids 1 to 52 of Figure 131 (SEQ ID NO:203), the native sequence PRO1006 is a full-length or mature native sequence PRO1006 comprising amino acids 1 or 24 through 392 of Figure 133 (SEQ ID NO:205), the native sequence PRO1112 polypeptide is a full-length or mature native sequence PRO1112 polypeptide comprising amino acids 1 or 14 through 262 of Figure 135 (SEQ ID NO:207), the native sequence PRO1074 polypeptide is a mature or full-length native sequence PRO1074 polypeptide comprising amino acids 1 to 331 of Figure 137 (SEQ ID NO:209), the native sequence PRO1005 is a full-length or mature native sequence PRO1005 comprising amino acids 1 or about 21 to 185 of Figure 139 (SEQ ID NO:211), the native sequence PRO1073 is a full-length or mature native sequence PRO1073 comprising amino acids 1 or about 32 to 299 of Figure 141 (SEQ ID NO:213), the native sequence PRO1152 is a mature or full-length native sequence PRO1152 comprising amino acids 1 to 479 of Figure 144 (SEQ ID NO:216), the native sequence PRO1136 is a mature or full-length native sequence PRO1136 comprising amino acids 1 to 632 of Figure 147 (SEQ ID NO:219), the native sequence PRO813 polypeptide is a mature or full-length native sequence PRO813 polypeptide comprising amino acids 1 to 76 of Figure 149 (SEQ ID NO:221), the native sequence PRO809 is a full-length or mature native sequence PRO809 comprising amino acids 1 or 19 through 265 of Figure 151 (SEQ ID NO:223), the native sequence PRO791 is a full-length or mature native sequence PRO791 comprising amino acids 1 or 26 through 246 of Figure 153 (SEQ ID NO:225), the native sequence PRO1004 is a full-length or mature native sequence PRO1004 comprising amino acids 1 or about 25 through 115 of Figure 155 (SEQ ID NO:227), the native sequence PRO1111 is a full-length or mature native sequence PRO1111 comprising amino acids 1 through 653 of Figure 157 (SEQ ID NO:229), the native sequence PRO1344 is a mature or full-length native sequence PRO1344 comprising amino acids 1 to 720 of Figure 159 (SEQ ID NO:231), the native sequence PRO1109 is a mature or full-length native sequence PRO1109 comprising amino acids 1 to 344 of Figure 161 (SEQ ID NO:236), the native sequence PRO1383 is a mature or full-length native sequence PRO1383 comprising amino acids 1 to 423 of Figure 163 (SEQ ID NO:241), the native sequence PRO1003 polypeptide is a mature or full-length native sequence PRO1003 polypeptide comprising amino acids

1 to 84 of Figure 165 (SEQ ID NO:246), the native sequence PRO1108 polypeptide is a mature or full-length native sequence PRO1108 polypeptide comprising amino acids 1 to 456 of Figure 167 (SEQ ID NO:248), the native sequence PRO1137 polypeptide is a mature or full-length native sequence PRO1137 polypeptide comprising amino acids 1 to 240 of Figure 169 (SEQ ID NO:250), the native sequence PRO1138 polypeptide is a mature or full-length native sequence PRO1138 polypeptide comprising amino acids 1 to 335 of Figure 171 (SEQ ID NO:253), the native sequence PRO1054 is a mature or full-length native sequence PRO1054 comprising amino acids 1 to 180 of Figure 174 (SEQ ID NO:256), the native sequence PRO994 is a mature or full-length native sequence PRO994 comprising amino acids 1 to 229 of Figure 176 (SEQ ID NO:258), the native sequence PRO812 is a mature or full-length native sequence PRO812 comprising amino acids 1 to 83 of Figure 178 (SEQ ID NO:260), the native sequence PRO1069 polypeptide is a mature or full-length native sequence PRO1069 polypeptide comprising amino acids 1 to 89 of Figure 180 (SEQ ID NO:262), the native sequence PRO1129 polypeptide is a mature or full-length native sequence PRO1129 polypeptide comprising amino acids 1 to 524 of Figure 182 (SEQ ID NO:264), the native sequence PRO1068 is a full-length or mature native sequence PRO1068 comprising amino acids 1 or about 21 to 124 of Figure 184 (SEQ ID NO:266), the native sequence PRO1066 polypeptide is a mature or full-length native sequence PRO1066 polypeptide comprising amino acids 1 to 117 of Figure 186 (SEQ ID NO:268), the native sequence PRO1184 polypeptide is a full-length or mature native sequence PRO1184 polypeptide comprising amino acids 1 or 39 through 142 of Figure 188 (SEQ ID NO:270), the native sequence PRO1360 is a full-length or mature native sequence PRO1360 comprising amino acids 1 or about 30 through 285 of Figure 190 (SEQ ID NO:272), the native sequence PRO1029 is a mature or full-length native sequence PRO1029 comprising amino acids 1 to 86 of Figure 192 (SEQ ID NO:274), the native sequence PRO1139 is a mature or full-length native sequence PRO1139 polypeptide comprising amino acids 1 to 131 or 29-131 of Figure 194 (SEQ ID NO:276), the native sequence PRO1309 is a full-length or mature native sequence PRO1309 comprising amino acids 1 or about 35 through 522 of Figure 196 (SEQ ID NO:278), the native sequence PRO1028 polypeptide is a full-length or mature native sequence PRO1028 polypeptide comprising amino acids 1 or 20 through 197 of Figure 198 (SEQ ID NO:281), the native sequence PRO1027 is a full-length or mature native sequence PRO1027 comprising amino acids 1 or 34 through 77 of Figure 200 (SEQ ID NO:283), the native sequence PRO1107 polypeptide is a full-length or mature native sequence PRO1107 polypeptide comprising amino acids 1 or 23 through 477 of Figure 202 (SEQ ID NO:285), the native sequence PRO1140 polypeptide is a mature or full-length native sequence PRO1140 polypeptide comprising amino acids 1 to 255 of Figure 204 (SEQ ID NO:287), the native sequence PRO1106 polypeptide is a full-length or mature native sequence PRO1106 polypeptide comprising amino acids 1 or 17 through 469 of Figure 206 (SEQ ID NO:289), the native sequence PRO1291 is a mature or full-length native sequence PRO1291 comprising amino acids 1 to 282 of Figure 208 (SEQ ID NO:291), the native sequence PRO1105 polypeptide is a full-length or mature native sequence PRO1105 polypeptide comprising amino acids 1 or 20 through 180 of Figure 210 (SEQ ID NO:293), the native sequence PRO1026 is a full-length or mature native sequence PRO1026 comprising amino acids 1 or 26 through 237 of Figure 212 (SEQ ID NO:295), the native sequence PRO1104 is a full-length or mature native sequence PRO1104 comprising amino acids 1 or about 23 through 341 of Figure 214 (SEQ ID NO:297), the native sequence PRO1100 is a full-length or mature native



sequence PRO1100 comprising amino acids 1 or 21 through 320 of Figure 216 (SEQ ID NO:299), the native sequence PRO836 is a full-length or mature native sequence PRO836 comprising amino acids 1 or 30 through 461 of Figure 218 (SEQ ID NO:301), the native sequence PRO1141 is a mature or full-length native sequence PRO1141 comprising amino acids 1 to 247 of Figure 220 (SEQ ID NO:303), the native sequence PRO1132 is a full-length or mature native sequence PRO1132 comprising amino acids 1 or about 23 through 293 of Figure 226 (SEQ ID NO:309), the native sequence NL7 is a mature or full-length native sequence NL7 comprising amino acids from about position 51 to about position 461 of Figure 228 (SEQ ID NO:314), the native sequence PRO1131 is a full-length or mature native sequence PRO1131 comprising amino acids 1 through 280 of Figure 230 (SEQ ID NO:319), the native sequence PRO1281 is a full-length or mature native sequence PRO1281 comprising amino acids 1 or about 16 to 775 of Figure 233 (SEQ ID NO:326), the native sequence PRO1064 is a mature or full-length native sequence PRO1064 comprising amino acids 1 to 153 of Figure 235 (SEQ ID NO:334), the native sequence PRO1379 is a full-length or mature native sequence PRO1379 comprising amino acids 1 or about 18 to 574 of Figure 238 (SEQ ID NO:340), the native sequence PRO844 is a full-length or mature native sequence PRO844 comprising amino acids 1 or 20 through 111 of Figure 240 (SEQ ID NO:344), the native sequence PRO848 is a full-length or mature native sequence PRO848 comprising amino acids 1 or 36 through 600 of Figure 242 (SEQ ID NO:347), the native sequence PRO1097 is a full-length or mature native sequence PRO1097 comprising amino acids 1 or 21 through 91 of Figure 244 (SEQ ID NO:349), the native sequence PRO1153 is a mature or full-length native sequence PRO1153 comprising amino acids 1 to 197 of Figure 246 (SEQ ID NO:351), the native sequence PRO1154 is a full-length or mature native sequence PRO1154 comprising amino acids 1 or 35 to 941 of Figure 248 (SEQ ID NO:353), the native sequence PRO1181 is a mature or full-length native sequence PRO1181 comprising amino acids 1 to 437 of Figure 250 (SEQ ID NO:355), the native sequence PRO1182 is a mature or full-length native sequence PRO1182 comprising amino acids 1 to 271 of Figure 252 (SEQ ID NO:357), the native sequence PRO1155 is a full-length native or mature sequence PRO1155 comprising amino acids 1 or 19 through 135 of Figure 254 (SEQ ID NO:359), the native sequence PRO1156 is a full-length or mature native sequence PRO1156 comprising amino acids 1 or about 23 to 159 of Figure 256 (SEQ ID NO:361), the native sequence PRO1098 is a full-length or mature native sequence PRO1098 comprising amino acids 1 or 20 through 78 of Figure 258 (SEQ ID NO:363), the native sequence PRO1127 is a full-length or mature native sequence PRO1127 comprising amino acids 1 or about 30 through 67 of Figure 260 (SEQ ID NO:365), the native sequence PRO1126 is a mature or full-length native sequence PRO1126 comprising amino acids 1 to 402 of Figure 262 (SEQ ID NO:367), the native sequence PRO1125 is a mature or full-length native sequence PRO1125 comprising amino acids 26 to 447 of Figure 264 (SEQ ID NO:369), the native sequence PRO1186 is a full-length or mature native sequence PRO1186 comprising amino acids 1 or about 20 through 105 of Figure 266 (SEQ ID NO:371), the native sequence PRO1198 is a full-length or mature native sequence PRO1198 comprising amino acids 1 or about 35 to 229 of Figure 268 (SEQ ID NO:373), the native sequence PRO1158 is a full-length or mature native sequence PRO1158 comprising amino acids 1 or about 20 to 123 of Figure 270 (SEQ ID NO:375), the native sequence PRO1159 is a mature or full-length native sequence PRO1159 comprising amino acids 1 to 90 of Figure 272 (SEQ ID NO:377), the native sequence PRO1124 is a mature or full-length native sequence PRO1124 comprising amino acids 22 through 919



of Figure 274 (SEQ ID NO:379), the native sequence PRO1287 is a mature or full-length native sequence PRO1287 comprising amino acids 1 to 532 of Figure 276 (SEQ ID NO:381), the native sequence PRO1312 is a full-length or mature native sequence PRO1312 comprising amino acids 1 or about 15 to 212 of Figure 278 (SEQ ID NO:387), the native sequence PRO1192 is a full-length or mature native sequence PRO1192 comprising amino acids 1 or about 22 to 215 of Figure 280 (SEQ ID NO:389), the native sequence PRO1160 is a mature or full-length native sequence PRO1160 comprising amino acids 1 to 90 of Figure 282 (SEQ ID NO:394), the native sequence PRO1187 is a full-length or mature native sequence PRO1187 comprising amino acids 1 or about 18 through 120 of Figure 284 (SEQ ID NO:399), the native sequence PRO1185 is a full-length or mature native sequence PRO1185 comprising amino acids 1 or about 22 through 198 of Figure 286 (SEQ ID NO:401), the native sequence PRO1345 is a mature or full-length native sequence PRO1345 comprising amino acids 1 to 206 of Figure 288 (SEQ ID NO:403), the native sequence PRO1245 is a full-length or mature native sequence PRO1245 comprising amino acids 1 or about 19 to 104 of Figure 290 (SEQ ID NO:408), the native sequence PRO1358 is a full-length or mature native sequence PRO1358 comprising amino acids 1 or about 19 through 444 of Figure 292 (SEQ ID NO:410), the native sequence PRO1195 is a full-length or mature native sequence PRO1195 comprising amino acids 1 or about 23 through 151 of Figure 294 (SEQ ID NO:412), the native sequence PRO1270 is a mature or full-length native sequence PRO1270 comprising amino acids 1 to 313 of Figure 296 (SEQ ID NO:414), the native sequence PRO1271 is a mature or full-length native sequence PRO1271 comprising amino acids 1 to 208 of Figure 298 (SEQ ID NO:416), the native sequence PRO1375 is a full-length or mature native sequence PRO1375 comprising amino acids 1 through 198 of Figure 300 (SEQ ID NO:418), the native sequence PRO1385 is a mature or full-length native sequence PRO1385 comprising amino acids 1 to 128 of Figure 302 (SEQ ID NO:420), the native sequence PRO1387 is a mature or full-length native sequence PRO1387 comprising amino acids 1 to 394 of Figure 304 (SEQ ID NO:422) and the native sequence PRO1384 is a full-length or mature native sequence PRO1384 comprising amino acids 1 to 229 of Figure 306 (SEQ ID NO:424). Start and stop codons are shown in bold font and underlined in the figures.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either or the transmembrane domain as initially identified.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO

polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, preferably at least about 81% amino acid sequence identity, more preferably at least about 82% amino acid sequence identity, more preferably at least about 83% amino acid sequence identity, more preferably at least about 84% amino acid sequence identity, more preferably at least about 85% amino acid sequence identity, more preferably at least about 86% amino acid sequence identity, more preferably at least about 87% amino acid sequence identity, more preferably at least about 88% amino acid sequence identity, more preferably at least about 89% amino acid sequence identity, more preferably at least about 90% amino acid sequence identity, more preferably at least about 91% amino acid sequence identity, more preferably at least about 92% amino acid sequence identity, more preferably at least about 93% amino acid sequence identity, more preferably at least about 94% amino acid sequence identity, more preferably at least about 95% amino acid sequence identity, more preferably at least about 96% amino acid sequence identity, more preferably at least about 97% amino acid sequence identity, more preferably at least about 98% amino acid sequence identity and most preferably at least about 99% amino acid sequence identity with the amino acid sequence of the full-length native amino acid sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, often at least about 20 amino acids in length, more often at least about 30 amino acids in length, more often at least about 40 amino acids in length, more often at least about 50 amino acids in length, more often at least about 60 amino acids in length, more often at least about 70 amino acids in length, more often at least about 80 amino acids in length, more often at least about 90 amino acids in length, more often at least about 100 amino acids in length, more often at least about 150 amino acids in length, more often at least about 200 amino acids in length, more often at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i.e., the sequence against which the PRO polypeptide of interest is being compared which may be

a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80% nucleic acid sequence identity, more preferably at least about 81% nucleic acid sequence identity, more preferably at least about 82% nucleic acid sequence identity, more preferably at least about 83% nucleic acid sequence identity, more preferably at least about 84% nucleic acid sequence identity, more preferably at least about 85% nucleic acid sequence identity, more preferably at least about 86% nucleic acid sequence identity, more preferably at least about 87% nucleic acid sequence identity, more preferably at least about 88% nucleic acid sequence identity, more preferably at least about 89% nucleic acid sequence identity, more preferably at least about 90% nucleic acid sequence identity, more preferably at least about 91% nucleic acid sequence identity, more preferably at least about 92% nucleic acid sequence identity, more preferably at least about 93% nucleic acid sequence identity, more preferably at least about 94% nucleic acid sequence identity, more preferably at least about 95% nucleic acid sequence identity, more preferably at least about 96% nucleic acid sequence identity, more preferably at least about 97% nucleic acid sequence identity, more preferably at least about 98% nucleic acid sequence identity and yet more preferably at least about 99% nucleic acid sequence identity with the nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, often at least about 60 nucleotides in length, more often at least about 90 nucleotides in length, more often at least about 120 nucleotides in length, more often at least about 150 nucleotides in length, more often at least about 180 nucleotides in length, more often at least about 210 nucleotides in length, more often at least about 240 nucleotides in length, more often at least about 270 nucleotides in length, more often at least about 300 nucleotides in length, more often at least about 450 nucleotides in length, more often at least about 600 nucleotides in length, more often at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR)



software. For purposes herein, however, % nucleic acid sequence identity values are generated using the WU-BLAST-2 computer program (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i.e., the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i.e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

The term "positives", in the context of sequence comparison performed as described above, includes residues in the sequences compared that are not identical but have similar properties (e.g. as a result of conservative substitutions, see Table 1 below). For purposes herein, the % value of positives is determined by dividing (a) the number of amino acid residues scoring a positive value between the PRO polypeptide amino acid sequence of interest having a sequence derived from the native PRO polypeptide sequence and the comparison amino acid sequence of interest (i.e., the amino acid sequence against which the PRO polypeptide sequence is being compared) as determined in the BLOSUM62 matrix of WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest.

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" PRO polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the PRO polypeptide nucleic acid. An isolated PRO polypeptide nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated PRO polypeptide nucleic acid molecules therefore are distinguished from the specific PRO polypeptide nucleic acid molecule as it exists in natural cells. However,



an isolated PRO polypeptide nucleic acid molecule includes PRO polypeptide nucleic acid molecules contained in cells that ordinarily express the PRO polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polyepitopic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M

sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

"Active" or "activity" for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically

include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

5 "Treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to  
10 an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats,  
15 rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often  
20 the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including  
25 glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, polyethylene glycol (PEG), and PLURONICS™.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')<sub>2</sub>, and Fv  
30 fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')<sub>2</sub> fragment that has two antigen-combining sites  
35 and is still capable of cross-linking antigen.



"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific  
5 for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge  
10 region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')<sub>2</sub> antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant  
15 domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2.

20 "Single-chain Fv" or "sFv" antibody fragments comprise the VH and VL domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

25 The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH - VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and  
30 Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1)  
35 to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or



nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

By "solid phase" is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small molecule" is defined herein to have a molecular weight below about 500 Daltons.

## II. Compositions and Methods of the Invention

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as "PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

### 1. Full-length PRO281 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO281 (UNQ244). In particular, cDNA encoding a PRO281

polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST-2 sequence alignment computer program, it has been found that a full-length native sequence PRO281 (shown in Figure 2 and SEQ ID NO:2) has certain amino acid sequence identity with the rat TEGT protein. Accordingly, it is presently believed that PRO281 disclosed in the present application is a newly identified TEGT homolog and may possess activity typical of that protein.

5

## 2. Full-length PRO276 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO276 (UNQ243). In particular, cDNA encoding a PRO276 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

10

As far as is known, the DNA16435-1208 sequence encodes a novel factor designated herein as PRO276; using WU-BLAST-2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed. The sequence identity identifications which were found are listed below in the examples.

## 3. Full-length PRO189 Polypeptides

15

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO189. In particular, Applicants have identified and isolated cDNA encoding a PRO189 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA21624-1391 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no significant sequence identities to any known proteins were revealed.

20

## 4. Full-length PRO190 Polypeptides

25

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO190. In particular, Applicants have identified and isolated cDNA encoding a PRO190 polypeptide, as disclosed in further detail in the Examples below. The PRO190-encoding clone was isolated from a human retina library. To Applicants present knowledge, the DNA23334-1392 nucleotide sequence encodes a novel multiple transmembrane spanning protein; using BLAST and FastA sequence alignment computer programs, there is some sequence identity with CMP-sialic acid and UDP-galactose transporters, indicating that PRO190 may be related to transporter or that PRO190 may be a novel transporter.

30

## 5. Full-length PRO341 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO341 (UNQ300). In particular, cDNA encoding a PRO341 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

35

The DNA26288-1239 clone was isolated from a human placenta library. As far as is known, the DNA26288-1239 sequence encodes a novel factor designated herein as PRO341; using the WU-BLAST-2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

#### 6. Full-length PRO180 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO180 (UNQ154). In particular, cDNA encoding a PRO180 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 The DNA26843-1389 clone was isolated from a human placenta library using oligos formed from DNA12922 isolated from an amylase screen. As far as is known, the DNA26843-1389 sequence encodes a novel factor designated herein as PRO180.

#### 7. Full-length PRO194 Polypeptides

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO194. In particular, Applicants have identified and isolated cDNA encoding a PRO194 polypeptide, as disclosed in further detail in the Examples below. The PRO194-encoding clone was isolated from a human fetal lung library. To Applicants present knowledge, the DNA26844-1394 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no significant sequence identities to any known proteins were revealed.

#### 8. Full-length PRO203 Polypeptides

15 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO203. In particular, Applicants have identified and isolated cDNA encoding a PRO203 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA  
20 sequence alignment computer programs, Applicants found that the PRO203 polypeptide has sequence identity with GST ATPase. Accordingly, it is presently believed that PRO203 polypeptide disclosed in the present application is a newly identified member of the ATPase family and possesses activity typical of the GST ATPase.

#### 9. Full-length PRO290 Polypeptides

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO290. In particular, cDNA encoding a PRO290 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 23 (SEQ ID NO:33), revealed sequence identities  
30 between the PRO290 amino acid sequence and the following Dayhoff sequences: P\_R99800, CC4H\_HUMAN, YCS2\_YEAST, CEF35G12\_13, HSFAN\_1, MMU52461\_1, MMU70015\_1, HSU67615\_1, CET01H10\_8 and CELT28F2\_6.

It is currently believed that PRO290 is an intracellular protein related to one or more of the above proteins.

#### 10. Full-length PRO874 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO874. In particular, Applicants have identified and isolated cDNA encoding a PRO874 polypeptide, as disclosed in further detail in the Examples below. The PRO874-encoding clone was isolated from a human fetal lung library. To Applicants present knowledge, the DNA40621-1440  
5 nucleotide sequence encodes a novel factor. Although, using BLAST and FastA sequence alignment computer programs, some sequence identity with known proteins was revealed.

#### 11. Full-length PRO710 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO710. In particular, Applicants have identified and isolated cDNA  
10 encoding a PRO710 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO710 polypeptide has significant similarity to the CDC45 protein. Accordingly, it is presently believed that PRO710 polypeptide disclosed in the present application is a newly identified CDC45 homolog.

#### 12. Full-length PRO1151 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1151. In particular, cDNA encoding a PRO1151 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST-2 sequence alignment computer program, it has been found that a full-length  
20 native sequence PRO1151 (shown in Figure 30 and SEQ ID NO:47) has certain amino acid sequence identity with the human 30 kD adipocyte complement-related precursor protein (ACR3\_HUMAN). Accordingly, it is presently believed that PRO1151 disclosed in the present application is a newly identified member of the complement protein family and may possess activity typical of that family.

#### 13. Full-length PRO1282 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1282. In particular, cDNA encoding a PRO1282 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA45495-1550 sequence encodes a novel factor designated herein as  
30 PRO1282. Using WU-BLAST-2 sequence alignment computer programs, some sequence identities between PRO1282 and other leucine rich repeat proteins were revealed, as discussed in the examples below, indicating that a novel member of the leucine rich repeat superfamily has been identified.

#### 14. Full-length PRO358 Polypeptides

The present invention further provides newly identified and isolated nucleotide sequences encoding a polypeptide referred to in the present application as PRO358. In particular, Applicants have identified and



isolated cDNA encoding a novel human Toll polypeptide (PRO358), as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the coding sequence of PRO358 shows significant homology to DNA sequences HSU88540\_1, HSU88878\_1, HSU88879\_1, HSU88880\_1, HS88881\_1, and HSU79260\_1 in the GenBank database. With the exception of HSU79260\_1, the noted proteins have been identified as human toll-like receptors.

5 Accordingly, it is presently believed that the PRO358 proteins disclosed in the present application are newly identified human homologues of the *Drosophila* protein Toll, and are likely to play an important role in adaptive immunity. More specifically, PRO358 may be involved in inflammation, septic shock, and response to pathogens, and play possible roles in diverse medical conditions that are aggravated by immune response, such as, for example, diabetes, ALS, cancer, rheumatoid arthritis, and ulcers. The role of PRO358 as pathogen  
10 pattern recognition receptors, sensing the presence of conserved molecular structures present on microbes, is further supported by the data disclosed in the present application, showing that a known human Toll-like receptor, TLR2 is a direct mediator of LPS signaling.

#### 15. Full-length PRO1310 Polypeptides

15 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1310. In particular, cDNA encoding a PRO1310 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST-2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1310 (shown in Figure 36 and SEQ ID NO:62) has certain amino acid sequence identity with  
20 carboxypeptidase X2. Accordingly, it is presently believed that PRO1310 disclosed in the present application is a newly identified member of the carboxypeptidase family and may possess carboxyl end amino acid removal activity.

#### 16. Full-length PRO698 Polypeptides

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO698. In particular, Applicants have identified and isolated cDNA encoding a PRO698 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO698 polypeptide has significant similarity to the olfactomedin protein. Accordingly, it is presently believed that PRO698 polypeptide disclosed in the  
30 present application may be a newly identified olfactomedin homolog.

#### 17. Full-length PRO732 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO732. In particular, Applicants have identified and isolated cDNA  
35 encoding a PRO732 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO732 polypeptide has significant similarity to the human placental Diff33 protein. Accordingly, it is presently believed that PRO732 polypeptide disclosed

in the present application is a newly identified Diff33 homolog.

#### 18. Full-length PRO1120 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1120. In particular, cDNA encoding a PRO1120 polypeptide has  
5 been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST-2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1120 (shown in Figure 47 and SEQ ID NO:84) has certain amino acid sequence identity with the known sulfatase proteins designated CELK09C4\_1, and GL6S\_HUMAN, respectively, in the Dayhoff database (version 35.45 SwissProt 35). Accordingly, it is presently believed that PRO1120 disclosed in the present  
10 application is a newly identified member of the sulfatase family and may possess activity typical of sulfatases.

#### 19. Full-length PRO537 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO537. In particular, cDNA encoding a PRO537 polypeptide has been  
15 identified and isolated, as disclosed in further detail in the Examples below. The DNA49141-1431 clone was isolated from a human placenta library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA49141-1431 clone does encode a secreted factor. As far as is known, the DNA49141-1431 sequence encodes a novel factor designated herein as PRO537; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were  
20 revealed.

#### 20. Full-length PRO536 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO536. In particular, cDNA encoding a PRO536 polypeptide has been  
25 identified and isolated, as disclosed in further detail in the Examples below.

The DNA49142-1430 clone was isolated from a human infant brain library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA49142-1430 clone does encode a secreted factor. As far as is known, the DNA49142-1430 sequence encodes a novel factor designated herein as PRO536; using the WU-BLAST-2 sequence alignment computer program, no significant sequence  
30 identities to any known proteins were revealed.

#### 21. Full-length PRO535 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO535. In particular, cDNA encoding a PRO535 polypeptide has been  
35 identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO535 (shown in Figure 53 and SEQ ID NO:99) has amino acid sequence identity with a

putative peptidyl-prolyl isomerase protein. Accordingly, it is presently believed that PRO535 disclosed in the present application is a newly identified member of the isomerase protein family and may possess activity typical of those proteins.

## **22. Full-length PRO718 Polypeptides**

5 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO718. In particular, Applicants have identified and isolated cDNA encoding a PRO718 polypeptide, as disclosed in further detail in the Examples below. The PRO718-encoding clone was isolated from a human fetal lung library. To Applicants present knowledge, the DNA49647-1398 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs,  
10 no significant sequence identities to any known proteins were revealed.

## **23. Full-length PRO872 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO872. In particular, Applicants have identified and isolated cDNA  
15 encoding a PRO872 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO872 polypeptide has sequence identity with dehydrogenases. Accordingly, it is presently believed that PRO872 polypeptide disclosed in the present application is a newly identified member of the dehydrogenase family and possesses dehydrogenase activity.

## **24. Full-length PRO1063 Polypeptides**

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1063. In particular, Applicants have identified and isolated cDNA encoding a PRO1063 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1063 polypeptide has significant  
25 similarity to the human type IV collagenase protein. Accordingly, it is presently believed that PRO1063 polypeptide disclosed in the present application is a newly identified collagenase homolog.

## **25. Full-length PRO619 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides  
30 referred to in the present application as PRO619. In particular, cDNA encoding a PRO619 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST-2 sequence alignment computer program, it has been found that a full-length native sequence PRO619 (shown in Figure 68 and SEQ ID NO:117) has certain amino acid sequence identity with VpreB3. Accordingly, it is presently believed that PRO619 disclosed in the present application is a newly  
35 identified member of the IgG superfamily and may possess activity related to the assembly and/or components of the surrogate light chain associated with developing B cells.

**26. Full-length PRO943 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO943. In particular, cDNA encoding a PRO943 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 Using the WU-BLAST-2 sequence alignment computer program, it has been found that a full-length native sequence PRO943 (shown in Figure 70 and SEQ ID NO:119) has amino acid sequence identity with the fibroblast growth factor receptor-4 protein. Accordingly, it is presently believed that PRO943 disclosed in the present application is a newly identified member of the fibroblast growth factor receptor family and may possess activity typical of that family.

**10 27. Full-length PRO1188 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1188. In particular, cDNA encoding a PRO1188 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

15 As discussed in more detail in Example 1 below, using WU-BLAST-2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1188 (shown in Figure 72; SEQ ID NO:124) has certain amino acid sequence identity with nucleotide pyrophosphohydrolase (SSU83114\_1). Accordingly, it is presently believed that PRO1188 disclosed in the present application is a newly identified member of the nucleotide pyrophosphohydrolase family and may possess activity typical of that family of proteins.

**20 28. Full-length PRO1133 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1133. In particular, cDNA encoding a PRO1133 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

25 Using WU-BLAST-2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1133 (shown in Figure 74 and SEQ ID NO:129) has certain amino acid sequence identity with netrin 1a, Dayhoff accession AF002717\_1. Accordingly, it is presently believed that PRO1133 disclosed in the present application shares at least one related mechanism with netrin.

**29. Full-length PRO784 Polypeptides**

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO784. In particular, cDNA, designated herein as "DNA53978-1443", which encodes a PRO784 polypeptide, has been identified and isolated, as disclosed in further detail in the Examples below.

35 Using BLAST and FastA sequence alignment computer programs, it has been found that a full-length native sequence PRO784 (shown in Figure 76 and SEQ ID NO:135) has certain amino acid sequence identity with sec22 homologs. Accordingly, it is presently believed that PRO784 disclosed in the present application is a newly identified member of the sec22 family and may possess vesicle trafficking activities typical of the sec22



family.

**30. Full-length PRO783 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO783. In particular, Applicants have identified and isolated cDNA encoding a PRO783 polypeptide, as disclosed in further detail in the Examples below. The PRO783-encoding clone was isolated from a human fetal kidney library. To Applicants present knowledge, the DNA53996-1442 nucleotide sequence encodes a novel factor. However, using BLAST and FastA sequence alignment computer programs, some sequence identity to known proteins was found.

**31. Full-length PRO820 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO820. In particular, Applicants have identified and isolated cDNA encoding a PRO820 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO820 polypeptide have sequence identity with the low affinity immunoglobulin gamma Fc receptor, the IgE high affinity Fc receptor and the high affinity immunoglobulin epsilon receptor. Accordingly, it is presently believed that PRO820 polypeptide disclosed in the present application is a newly identified member of the Fc receptor family.

**32. Full-length PRO1080 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1080. In particular, Applicants have identified and isolated cDNA encoding a PRO1080 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Dayhoff database (version 35.45 SwissProt 35), Applicants found that the PRO1080 polypeptide has sequence identity with a 39.9 kd protein designated as "YRY1\_CAEL", a DnaJ homolog designated "AF027149\_5", a DnaJ homolog 2 designated "RNU95727\_1", and Dna3/Cpr3 designated "AF011793\_1". Accordingly, these results indicate that the PRO1080 polypeptide disclosed in the present application may be a newly identified member of the DnaJ-like protein family and therefore may be involved in protein biogenesis.

**33. Full-length PRO1079 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1079. In particular, cDNA encoding a PRO1079 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA56050-1455 sequence encodes a novel factor designated herein as PRO1079. Although, using WU-BLAST2 sequence alignment computer programs, some sequence identities to known proteins was revealed.

**34. Full-length PRO793 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO793. In particular, cDNA encoding a PRO793 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 The DNA56110-1437 clone was isolated from a human skin tumor library. As far as is known, the DNA56110-1437 sequence encodes a novel factor designated herein as PRO793; using the WU-BLAST-2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

**35. Full-length PRO1016 Polypeptides**

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1016. In particular, Applicants have identified and isolated cDNA encoding a PRO1016 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1016 polypeptide have sequence identity with acyltransferases. Accordingly, it is presently believed that PRO1016 polypeptide disclosed in the present application is a newly identified member of the acyltransferase family and  
15 possesses acylation capabilities typical of this family.

**36. Full-length PRO1013 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1013. In particular, Applicants have identified cDNA encoding a  
20 PRO1013 polypeptide, as disclosed in further detail in the Examples below. The PRO1013-encoding clone came from a human breast tumor tissue library. Thus, the PRO1013-encoding clone may encode a secreted factor related to cancer. To Applicants present knowledge, the DNA56410-1414 nucleotide sequence encodes a novel factor. Using BLAST and FastA sequence alignment computer programs, some sequence identity with KIAA0157 and P120 was revealed. PRO1013 has at least one region in common with growth factor and  
25 cytokine receptors.

**37. Full-length PRO937 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO937. In particular, Applicants have identified and isolated cDNA  
30 encoding a PRO937 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO937 polypeptide has significant sequence identity with members of the glypican family of proteins. Accordingly, it is presently believed that PRO937 polypeptide disclosed in the present application is a newly identified member of the glypican family possesses properties typical of the glypican family.

35

**38. Full-length PRO842 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO842. In particular, cDNA encoding a PRO842 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 As far as is known, the DNA56855-1447 sequence encodes a novel secreted factor designated herein as PRO842. However, using WU-BLAST2 sequence alignment computer programs, some sequence identity to any known proteins were revealed.

**39. Full-length PRO839 Polypeptides**

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO839. In particular, cDNA encoding a PRO839 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA56859-1445 sequence encodes a novel factor designated herein as PRO839. However, using WU-BLAST-2 sequence alignment computer programs, some sequence identities to known proteins was revealed.

**40. Full-length PRO1180 Polypeptides**

15 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1180. In particular, Applicants have identified and isolated cDNA encoding a PRO1180 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and  
20 FastA sequence alignment computer programs, Applicants found that the PRO1180 polypeptide has significant similarity to methyltransferase enzymes. Accordingly, it is presently believed that PRO1180 polypeptide disclosed in the present application is a newly identified member of the methyltransferase family and possesses activity typical of that family.

**41. Full-length PRO1134 Polypeptides**

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1134. In particular, cDNA encoding a PRO1134 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

30 The DNA56865-1491 clone was isolated from a human fetal liver spleen library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA56865-1491 clone does encode a secreted factor. As far as is known, the DNA56865-1491 sequence encodes a novel factor designated herein as PRO1134; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

**42. Full-length PRO830 Polypeptides**

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO830. In particular, cDNA encoding a PRO830 polypeptide has been

identified and isolated, as disclosed in further detail in the Examples below.

The DNA56866-1342 clone was isolated from a human fetal liver/spleen library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA56866-1342 clone does encode a secreted factor. As far as is known, the DNA56866-1342 sequence encodes a novel factor designated herein as PRO830; using the WU-BLAST-2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

#### **43. Full-length PRO1115 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1115. In particular, cDNA encoding a PRO1115 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA56868-1478 sequence encodes a novel transmembrane protein designated herein as PRO1115. Although, using WU-BLAST-2 sequence alignment computer programs, some sequence identities to known proteins were revealed.

#### **44. Full-length PRO1277 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1277. In particular, cDNA encoding a PRO1277 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST-2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1277 (shown in Figure 113 and SEQ ID NO:179) has certain amino acid sequence identity with Coch-5B2 protein (designated "AF012252\_1" in the Dayhoff database). Accordingly, it is presently believed that PRO1277 disclosed in the present application is a newly identified member of the Coch-5B2 protein family and may possess the same activities and properties as Coch-5B2.

#### **45. Full-length PRO1135 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1135. In particular, Applicants have identified and isolated cDNA encoding a PRO1135 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1135 polypeptide has significant similarity to the alpha 1,2-mannosidase protein. Accordingly, it is presently believed that PRO1135 polypeptide disclosed in the present application is a newly identified member of the mannosidase enzyme family and possesses activity typical of that family of proteins.

#### **46. Full-length PRO1114 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1114 interferon receptor. In particular, cDNA encoding a PRO1114 interferon receptor polypeptide has been identified and isolated, as disclosed in further detail in the Examples



below.

Using the WU-BLAST-2 sequence alignment computer program, it has been found that a full-length native sequence PRO1114 interferon receptor polypeptide (shown in Figure 117 and SEQ ID NO:183) has sequence identity with the other known interferon receptors. Accordingly, it is presently believed that PRO1114 interferon receptor possesses activity typical of other interferon receptors.

5

**47. Full-length PRO828 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO828. In particular, Applicants have identified and isolated cDNA encoding a PRO828 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO828 polypeptide has sequence identity with glutathione peroxidases. Accordingly, it is presently believed that PRO828 polypeptide disclosed in the present application is a newly identified member of the glutathione peroxidase family and possesses peroxidase activity and other properties typical of glutathione peroxidases.

10

**48. Full-length PRO1009 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1009. In particular, cDNA encoding a PRO1009 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

15

Using WU-BLAST-2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1009 (shown in Figure 122 and SEQ ID NO:194) has certain amino acid sequence identity with long-chain acyl-CoA synthetase homolog designated "F69893". Accordingly, it is presently believed that PRO1009 disclosed in the present application is a newly identified member of the long-chain acyl-CoA synthetase family and may possess activity related to this family.

20

**49. Full-length PRO1007 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1007. In particular, Applicants have identified and isolated cDNA encoding a PRO1007 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that various portions of the PRO1007 polypeptide have sequence identity with MAGPIAP. Accordingly, it is presently believed that PRO1007 polypeptide disclosed in the present application is a newly identified member of the MAGPIAP family and is associated with metastasis and/or cell signaling and/or cell replication.

25

**50. Full-length PRO1056 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1056. In particular, cDNA encoding a PRO1056 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

30

35

Using the WU-BLAST-2 sequence alignment computer program, it has been found that a full-length native sequence PRO1056 (shown in Figure 127 and SEQ ID NO:199) has amino acid sequence identity with a chloride channel protein. Accordingly, it is presently believed that PRO1056 disclosed in the present application is a newly identified chloride channel protein homolog.

5                   **51.     Full-length PRO826 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO826. In particular, cDNA encoding a PRO826 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

10           The DNA57694-1341 clone was isolated from a human fetal heart library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA57694-1341 clone does encode a secreted factor. As far as is known, the DNA57694-1341 sequence encodes a novel factor designated herein as PRO826; using the WU-BLAST-2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

15                   **52.     Full-length PRO819 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO819. In particular, cDNA encoding a PRO819 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

20           The DNA57695-1340 clone was isolated from a human fetal liver spleen library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA57695-1340 clone does encode a secreted factor. As far as is known, the DNA57695-1340 sequence encodes a novel factor designated herein as PRO819; using the WU-BLAST-2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

25                   **53.     Full-length PRO1006 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1006. In particular, Applicants have identified and isolated cDNA encoding a PRO1006 polypeptide, as disclosed in further detail in the Examples below. The PRO1006-encoding clone was isolated from a human uterus library. To Applicants present knowledge, the DNA57699-1412  
30           nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, some sequence identity with a putative tyrosine protein kinase was revealed.

**54.     Full-length PRO1112 Polypeptides**

35           The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1112. In particular, Applicants have identified cDNA encoding a PRO1112 polypeptide, as disclosed in further detail in Example 1 below. To Applicants present knowledge, the DNA57702-1476 nucleotide sequence encodes a novel factor, although using BLAST and FastA sequence

alignment computer programs some sequence identity with other known proteins was found.

**55. Full-length PRO1074 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1074. In particular, Applicants have identified and isolated cDNA encoding a PRO1074 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1074 polypeptide has sequence identity with galactosyltransferase. Accordingly, it is presently believed that PRO1074 polypeptide disclosed in the present application is a newly identified member of the galactosyltransferase family and possesses galactosyltransferase activity.

**56. Full-length PRO1005 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1005. In particular, cDNA encoding a PRO1005 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA57708-1411 sequence encodes a novel factor designated herein as PRO1005. However, using WU-BLAST2 sequence alignment computer programs, some sequence identities with known proteins was revealed.

**57. Full-length PRO1073 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1073. In particular, cDNA encoding a PRO1073 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA57710 sequence encodes a novel secreted factor designated herein as PRO1073. However, using WU-BLAST2 sequence alignment computer programs, some sequence identities to known proteins were revealed.

**58. Full-length PRO1152 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1152. In particular, cDNA encoding a PRO1152 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA57711-1501 clone was isolated from a human infant brain library. As far as is known, the DNA57711-1501 sequence encodes a novel factor designated herein as PRO1152; using the WU-BLAST-2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

**59. Full-length PRO1136 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1136. In particular, cDNA encoding a PRO1136 polypeptide has

been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1136 (shown in Figure 147 and SEQ ID NO:219) has amino acid sequence identity with PDZ domain-containing proteins. Accordingly, it is presently believed that PRO1136 disclosed in the present application is a newly identified member of the PDZ domain-containing protein family and may possess activity typical of that family.

**60. Full-length PRO813 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO813. In particular, Applicants have identified and isolated cDNA encoding a PRO813 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO813 polypeptide has significant similarity to the pulmonary surfactant-associated protein C. Accordingly, it is presently believed that PRO813 polypeptide disclosed in the present application is a newly identified pulmonary surfactant-associated protein C homolog.

**61. Full-length PRO809 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO809. In particular, Applicants have identified and isolated cDNA encoding a PRO809 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA57836-1338 nucleotide sequence encodes a novel factor.

**62. Full-length PRO791 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO791. In particular, Applicants have identified and isolated cDNA encoding a PRO791 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA57838-1337 nucleotide sequence encodes a novel factor; however, using BLAST and FastA sequence alignment computer programs, there does appear to be some sequence identity with MHC-1 antigens, indicating that PRO791 may be related thereto in structure and function.

**63. Full-length PRO1004 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1004. In particular, cDNA encoding a PRO1004 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA57844-1410 sequence encodes a novel factor designated herein as PRO1004. However, using WU-BLAST2 sequence alignment computer programs, some sequence identities with known proteins were revealed.



**64. Full-length PRO1111 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1111. In particular, cDNA encoding a PRO1111 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1111 (shown in Figure 157 and SEQ ID NO:229) has certain amino acid sequence identity with LIG. Accordingly, it is presently believed that PRO1111 disclosed in the present application is a newly identified member of this glycoprotein family.

**65. Full-length PRO1344 Polypeptides**

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1344. In particular, cDNA encoding a PRO1344 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1344 (shown in Figure 159 and SEQ ID NO:231) has certain amino acid sequence identity  
15 with the factor C protein of Carinoscorpius rotundicauda. Accordingly, it is presently believed that PRO1344 disclosed in the present application is a newly identified factor C protein and may possess activity typical of that protein.

**66. Full-length PRO1109 Polypeptides**

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1109. In particular, cDNA encoding a PRO1109 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1109 (shown in Figure 161 and SEQ ID NO:236) has certain amino acid sequence identity  
25 with the human UDP-Gal:GlcNAc galactosyltransferase protein. Accordingly, it is presently believed that PRO1109 disclosed in the present application is a newly identified  $\beta$ -galactosyltransferase enzyme and has activity typical of those enzymes.

**67. Full-length PRO1383 Polypeptides**

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1383. In particular, cDNA encoding a PRO1383 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1383 (shown in Figure 163 and SEQ ID NO:241) has certain amino acid sequence identity  
35 with the putative human transmembrane protein nmb precursor (NMB\_HUMAN). Accordingly, it is presently believed that PRO1383 disclosed in the present application is a newly identified nmb homolog.

**68. Full-length PRO1003 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1003. In particular, Applicants have identified and isolated cDNA encoding a PRO1003 polypeptide, as disclosed in further detail in the Examples below. The PRO1003-encoding clone was isolated from a human breast tumor tissue library. The PRO1003-encoding clone was isolated using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the PRO1003-encoding clone may encode a secreted factor. To Applicants present knowledge, the UNQ487 (DNA58846-1409) nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no sequence identities to any known proteins were revealed.

**69. Full-length PRO1108 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1108. In particular, Applicants have identified and isolated cDNA encoding a PRO1108 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1108 polypeptide has significant similarity to the LPAAT protein. Accordingly, it is presently believed that PRO1108 polypeptide disclosed in the present application is a newly identified LPAAT homolog.

**70. Full-length PRO1137 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1137. In particular, Applicants have identified and isolated cDNA encoding a PRO1137 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1137 polypeptide has sequence identity with ribosyltransferases. Accordingly, it is presently believed that PRO1137 polypeptide disclosed in the present application is a newly identified member of the ribosyltransferase family and possesses ribosyltransferase activity.

**71. Full-length PRO1138 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1138. In particular, Applicants have identified and isolated cDNA encoding a PRO1138 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1138 polypeptide has sequence identity with CD84 leukocyte antigen. Accordingly, it is presently believed that PRO1138 polypeptide disclosed in the present application is a newly identified member of the Ig superfamily and has activity typical of other members of the Ig superfamily.

**72. Full-length PRO1054 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1054. In particular, cDNA encoding a PRO1054 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1054 (shown in Figure 174 and SEQ ID NO:256) has amino acid sequence identity with one or more of the major urinary proteins. Accordingly, it is presently believed that PRO1054 disclosed in the present application is a newly identified member of the MUP family and may possess activity typical of that family.

**10 73. Full-length PRO994 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO994. In particular, cDNA encoding a PRO994 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

15 Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO994 (shown in Figure 176 and SEQ ID NO:258) has amino acid sequence identity with the tumor-associated antigen L6. Accordingly, it is presently believed that PRO994 disclosed in the present application is a newly identified L6 antigen homolog.

**20 74. Full-length PRO812 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO812. In particular, cDNA encoding a PRO812 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

25 Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO812 (shown in Figure 178 and SEQ ID NO:260) has amino acid sequence identity with the prostatic steroid-binding c1 protein. Accordingly, it is presently believed that PRO812 disclosed in the present application is a newly identified prostatic steroid-binding c1 protein homolog.

**75. Full-length PRO1069 Polypeptides**

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1069. In particular, Applicants have identified and isolated cDNA encoding a PRO1069 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, it was found that the PRO1069 polypeptide has sequence identity with CHIF. Accordingly, it is presently believed that PRO1069 polypeptide disclosed in the present application is a newly identified CHIF polypeptide and is involved in ion conductance or regulation of ion conductance.

35

**76. Full-length PRO1129 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1129. In particular, Applicants have identified and isolated cDNA encoding a PRO1129 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1129 polypeptide has significant similarity to the cytochrome P-450 family of proteins. Accordingly, it is presently believed that PRO1129 polypeptide disclosed in the present application is a newly identified member of the cytochrome P-450 family and possesses activity typical of that family.

**77. Full-length PRO1068 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1068. In particular, cDNA encoding a PRO1068 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1068 has amino acid sequence identity with urotensin. Accordingly, it is presently believed that PRO1068 disclosed in the present application is a newly identified member of the urotensin family and may possess activity typical of the urotensin family.

**78. Full-length PRO1066 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1066. In particular, Applicants have identified and isolated cDNA encoding a PRO1066 polypeptide, as disclosed in further detail in the Examples below. The PRO1066-encoding clone was isolated from a human pancreatic tumor tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the PRO1066-encoding clone may encode a secreted factor. To Applicants present knowledge, the DNA59215-1425 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no sequence identities to any known proteins were revealed.

**79. Full-length PRO1184 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1184. In particular, Applicants have identified cDNA encoding a PRO1184 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59220-1514 nucleotide sequence encodes a novel secreted factor.

**80. Full-length PRO1360 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1360. In particular, cDNA encoding a PRO1360 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.



As far as is known, the DNA59488-1603 sequence encodes a novel factor designated herein as PRO1360; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed. Some sequence identities were revealed, as indicated below in the examples.

#### 81. Full-length PRO1029 Polypeptides

5 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1029. In particular, cDNA encoding a PRO1029 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

10 The DNA59493-1420 clone was isolated from a human fetal liver spleen library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA59493-1420 clone does encode a secreted factor. As far as is known, the DNA59493-1420 sequence encodes a novel factor designated herein as PRO1029; using the WU-BLAST2 sequence alignment computer program, no sequence identities to any known proteins were revealed.

#### 82. Full-length PRO1139 Polypeptides

15 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1139. In particular, Applicants have identified and isolated cDNAs encoding PRO1139, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the human PRO1139 protein originally identified exhibits a significant sequence homology to the a OB receptor associated protein HSOBRGRP\_1, described by Bailleul  
20 et al., Nucleic Acids Res. 25, 2752-2758 (1997) (EMBL Accession No: Y12670).

#### 83. Full-length PRO1309 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1309. In particular, cDNA encoding a PRO1309 polypeptide has  
25 been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1309 (shown in Figure 196 and SEQ ID NO:278) has certain amino acid sequence identity with a protein designated KIAA0416, given the Dayhoff designation AB007876\_1. Moreover, PRO1309 has leucine rich repeats, accordingly, it is presently believed that PRO1309 disclosed in the present application is  
30 a newly identified member of the leucine rich protein family and may be involved in protein protein interactions.

#### 84. Full-length PRO1028 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1028. In particular, Applicants have identified and isolated cDNA  
35 encoding a PRO1028 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59603-1419 nucleotide sequence encodes a novel factor. BLAST and FastA sequence alignment computer programs showed some sequence identity with proteins such as those designated "A53050"

**85. Full-length PRO1027 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1027. In particular, Applicants have identified and isolated cDNA  
5 encoding a PRO1027 polypeptide, as disclosed in further detail in the Examples below. The PRO1027-encoding clone was identified in a human uterine cervical tissue library. To Applicants present knowledge, the DNA59605-1418 nucleotide sequence encodes a novel factor.

**86. Full-length PRO1107 Polypeptides**

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1107. In particular, Applicants have identified and isolated cDNA encoding a PRO1107 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1107 polypeptide has some  
15 similarity to the PC-1 protein, human insulin receptor tyrosine kinase inhibitor, an alkaline phosphodiesterase, and autotaxin. Accordingly, it is presently believed that PRO1107 polypeptide disclosed in the present application is a newly identified member of the phosphodiesterase family.

**87. Full-length PRO1140 Polypeptides**

20 The present invention provides newly identified and isolated nucleotide sequences encoding novel multi-span transmembrane polypeptides referred to in the present application as PRO1140. In particular, Applicants have identified and isolated cDNA encoding a PRO1140 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, some sequence identity with known proteins was found.

**88. Full-length PRO1106 Polypeptides**

25 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1106. In particular, Applicants have identified and isolated cDNA encoding a PRO1106 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO1106 polypeptide has significant  
30 similarity to the peroxisomal calcium-dependent solute carrier. Accordingly, it is presently believed that PRO1106 polypeptide disclosed in the present application is a newly identified member of the mitochondrial carrier superfamily and possesses transporter activity typical of this family.

**89. Full-length PRO1291 Polypeptides**

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1291. In particular, cDNA encoding a PRO1291 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1291 (shown in Figure 208 and SEQ ID NO:291) has certain amino acid sequence identity with the butyrophilin protein. Accordingly, it is presently believed that PRO1291 disclosed in the present application is a newly identified butyrophilin homolog and may possess activity typical of that protein.

5                   **90.     Full-length PRO1105 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1105. In particular, Applicants have identified cDNA encoding a PRO1105 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59612-1466 nucleotide sequence encodes a novel factor. There is, however, some sequence identity  
10 with a peroxylase precursor designated in a Dayhoff database as "ATTS1623\_1".

**91.     Full-length PRO511 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO511. In particular, Applicants have identified and isolated cDNA  
15 encoding a PRO511 polypeptide, as disclosed in further detail in the Examples below. The PRO511-encoding clone was isolated from a human colon tissue library. To Applicants present knowledge, the DNA59613-1417 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, sequence identities with RoBo-1, phospholipase inhibitors and a protein designated as "SSC20F10\_1" were revealed, indicated that PRO511 may be related to one or more of these proteins.

20

**92.     Full-length PRO1104 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1104. In particular, Applicants have identified and isolated cDNA encoding a PRO1104 polypeptide, as disclosed in further detail in the Examples below. To Applicants present  
25 knowledge, the DNA59616-1465 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, some sequence identity appeared with proteins designated as "AB002107\_1", "AF022991\_1" and "SP96\_DICDI".

**93.     Full-length PRO1100 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1100. In particular, Applicants have identified cDNA encoding a PRO1100 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59619-1464 nucleotide sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, only some sequence identity with known proteins was revealed. There is some sequence  
35 identity with the yeast hypothetical 42.5 KD protein in TSM1-ARE1 intergenic region (ACCESSION NO:140496), designated "YSCT4\_YEAST".

**94. Full-length PRO836 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO836. In particular, Applicants have identified and isolated cDNA encoding a PRO836 polypeptide, as disclosed in further detail in the Examples below. To Applicants present knowledge, the DNA59620-1463 nucleotide sequence encodes a novel factor. Using BLAST and FastA  
5 sequence alignment computer programs, there appears to be some sequence identity with SLS1.

**95. Full-length PRO1141 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1141. In particular, cDNA encoding a PRO1141 polypeptide has  
10 been identified and isolated, as disclosed in further detail in the Examples below.

The DNA59625-1498 clone was isolated from a human ileum tissue library. As far as is known, the DNA59625-1498 sequence encodes a novel factor designated herein as PRO1141; using the WU-BLAST2 sequence alignment computer program, no sequence identities to any known proteins were revealed.

**96. Full-length PRO1132 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1132. In particular, cDNA encoding a PRO1132 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer program, it has been found that a full-length native  
20 sequence PRO1132 (shown in Figure 226 and SEQ ID NO:309) has certain amino acid sequence identity with enamel matrix serine proteinase 1 and neuropsin. Accordingly, it is presently believed that PRO1132 disclosed in the present application is a newly identified member of the serine protease family and may possess protease activity typical of this family.

**97. Full-length PRO1346 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as NL7 (UNQ701). In particular, cDNA encoding an NL7 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As disclosed in the Examples below, a clone DNA59776-1600 has been deposited with ATCC. The  
30 actual nucleotide sequence of the clone can be readily determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the NL7 (PRO1346) herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time of filing.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native  
35 sequence NL7 (shown in Figure 228 and SEQ ID NO:314) has certain amino acid sequence identity with microfibril-associated glycoprotein 4 (MFA4\_HUMAN); ficolin-A - Mus musculus (AB007813\_1); human lectin P35 (D63155S6\_1); ficolin B - Mus musculus (AFO063217\_1); human tenascin-R (restriction) (HS518E13\_1);



the long form of a rat janusin precursor (A45445); fibrinogen-related protein HFREP-1 precursor (JNO596); a human Tenascin precursor (TENA HUMAN); human CDT6 (HSY16132\_1); and angiopoietin-1 - Mus musculus (MMU83509\_1). It is presently believed that NL7 disclosed in the present application is a novel TIE ligand homologue, and may play a role in angiogenesis and/or vascular maintenance and/or wound healing and/or inflammation and/or tumor development and/or growth

5  
98. **Full-length PRO1131 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1131. In particular, cDNA encoding a PRO1131 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

10 Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1131 (shown in Figure 230 and SEQ ID NO:319) has certain amino acid sequence identity with a lectin-like oxidized LDL receptor. Accordingly, it is presently believed that PRO1131 disclosed in the present application may have at least one mechanism similar to those of the LDL receptors.

15  
99. **Full-length PRO1281 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1281. In particular, cDNA encoding a PRO1281 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

20 The DNA59820-1549 clone was isolated from a human fetal liver library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, as far as is known, the DNA59820-1549 sequence encodes a novel factor designated herein as PRO1281. Using WU-BLAST2 sequence alignment computer programs, some sequence identities to known proteins was found, but determined not to be significant.

25  
100. **Full-length PRO1064 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1064. In particular, cDNA encoding a PRO1064 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

30 The DNA59827-1426 clone was isolated from a human fetal kidney library. As far as is known, the DNA59827-1426 sequence encodes a novel factor designated herein as PRO1064; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

101. **Full-length PRO1379 Polypeptides**

35 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1379. In particular, cDNA encoding a PRO1379 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA59828 clone was isolated from a human fetal kidney library. As far as is known, the PRO1379 polypeptide encoded thereby is a novel secreted factor. Using WU-BLAST2 sequence alignment

computer programs, sequence identity was found between PRO1379 and a hypothetical yeast protein "YHY8\_YEAST" (Dayhoff database; version 35.45 SwissProt 35), particularly at the C-terminal ends. Sequence homologies with other known proteins were revealed, but determined not to be significant.

#### 102. Full-length PRO844 Polypeptides

5 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO844. In particular, Applicants have identified and isolated cDNA encoding a PRO844 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO844 polypeptide has sequence identity with serine protease inhibitors. Accordingly, it is presently believed that PRO844 polypeptide disclosed in the  
10 present application is a newly identified serine protease inhibitor and is capable of inhibiting serine proteases.

#### 103. Full-length PRO848 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO848. In particular, Applicants have identified and isolated cDNA  
15 encoding a PRO848 polypeptide, as disclosed in further detail in the Examples below. Using BLAST and FastA sequence alignment computer programs, Applicants found that the PRO848 polypeptide has sequence identity with sialyltransferases. Accordingly, it is presently believed that PRO848 polypeptide disclosed in the present application is a newly identified member of the sialyltransferase family and possesses sialylation capabilities as typical of this family.

20

#### 104. Full-length PRO1097 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1097. In particular, Applicants have identified and isolated cDNA encoding a PRO1097 polypeptide, as disclosed in further detail in the Examples below. To Applicants present  
25 knowledge, the DNA59841-1460 nucleotide sequence encodes a novel factor. Using BLAST and FastA sequence alignment computer programs, some sequence identity with proteins designated as "CELK05G3\_3", "CRU26344\_1", "SPBC16C6\_8", "P\_W13844" and "AF013403" was revealed.

#### 105. Full-length PRO1153 Polypeptides

30 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1153. In particular, cDNA encoding a PRO1153 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1153 (shown in Figure 246 and SEQ ID NO:351) has certain amino acid sequence identity with  
35 HPBR11-7 protein submitted to the EMBL Data Library June 1992. Accordingly, it is presently believed that PRO1153 disclosed in the present application may be related to HPBR11-7.

**106. Full-length PRO1154 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1154. In particular, cDNA encoding a PRO1154 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1154 (shown in Figure 248 and SEQ ID NO:353) aligns with a KIAA0525 protein, designated AB011097. PRO1154 has a novel N-terminus of 73 amino acids. Accordingly, PRO1154 is believed to be novel. PRO1154 also has significant sequence identity with aminopeptidase N, insulin-regulated membrane aminopeptidase, throtropin-releasing hormone degrading enzyme and placental leucine aminopeptidase. Therefore, PRO1154 is believed to be a novel aminopeptidase, or peptide which degrades peptides.

**107. Full-length PRO1181 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1181. In particular, cDNA encoding a PRO1181 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA59847-1511 clone was isolated from a human prostate tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA59847-1511 clone does encode a secreted factor. As far as is known, the DNA59847-1511 sequence encodes a novel factor designated herein as PRO1181; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

**108. Full-length PRO1182 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1182. In particular, cDNA encoding a PRO1182 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1182 (shown in Figure 252 and SEQ ID NO:357) has amino acid sequence identity with the conglutinin protein. Accordingly, it is presently believed that PRO1182 disclosed in the present application is a newly identified conglutinin homolog.

**109. Full-length PRO1155 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1155. In particular, cDNA encoding a PRO1155 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1155 (shown in Figure 254 and SEQ ID NO:359) has certain amino acid sequence identity with neurokinin B. Accordingly, it is presently believed that PRO1155 disclosed in the present application is a newly identified member of the tachykinin family.

**110. Full-length PRO1156 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1156. In particular, cDNA encoding a PRO1156 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 The DNA59853-1505 clone was isolated from an adult human heart library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA59853-1505 clone may encode a secreted factor. As far as is known, the DNA59853-1505 sequence encodes a novel factor designated herein as PRO1156. However, using WU-BLAST2 sequence alignment computer programs, some sequence identity with known proteins were revealed.

**10 111. Full-length PRO1098 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1098. In particular, Applicants have identified cDNA encoding a PRO1098 polypeptide, as disclosed in further detail in the Examples below. The PRO1098-encoding clone was isolated from a human lung tissue library. To Applicants present knowledge, the DNA59854-1459 nucleotide  
15 sequence encodes a novel factor; using BLAST and FastA sequence alignment computer programs, no significant sequence identities to any known proteins were revealed. Some sequence identity appeared with proteins such as the "Env" polyprotein and a methyltransferase.

**112. Full-length PRO1127 Polypeptides**

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1127. In particular, cDNA encoding a PRO1127 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA60283-1484 clone encodes a secreted factor. As far as is known, the DNA60283-1484 sequence encodes a novel factor designated herein as PRO1127; using WU-BLAST2 sequence alignment  
25 computer programs, minimal sequence identities to any known proteins were revealed.

**113. Full-length PRO1126 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1126. In particular, cDNA encoding a PRO1126 polypeptide has  
30 been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1126 (shown in Figure 262 and SEQ ID NO:367) has certain amino acid sequence identity with the olfactomedin protein. Accordingly, it is presently believed that PRO1126 disclosed in the present application is a newly identified olfactomedin homolog and may possess activity typical of that protein.

35



**114. Full-length PRO1125 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1125. In particular, cDNA encoding a PRO1125 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

5 Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1125 (shown in Figure 264 and SEQ ID NO:369) has certain amino acid sequence identity with transcriptional repressor rco-1. Accordingly, it is presently believed that PRO1125 disclosed in the present application is a newly identified member of the WD superfamily.

**115. Full-length PRO1186 Polypeptides**

10 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1186. In particular, cDNA encoding a PRO1186 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1186 (shown in Figure 266 and SEQ ID NO:371) has amino acid sequence identity with venom  
15 protein A from Dendroaspis polylepsis polylepsis venom. Accordingly, it is presently believed that PRO1186 disclosed in the present application is a newly identified member of venom protein A and may share a related mechanism.

**116. Full-length PRO1198 Polypeptides**

20 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1198. In particular, cDNA encoding a PRO1198 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA60622-1525 sequence encodes a novel factor designated herein as PRO1198. However, using WU-BLAST2 sequence alignment computer programs, some sequence identity with  
25 known proteins was found.

**117. Full-length PRO1158 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1158. In particular, cDNA encoding a PRO1158 polypeptide has  
30 been identified and isolated, as disclosed in further detail in the Examples below.

The DNA60625-1507 clone was isolated from a human lung tumor tissue library. As far as is known, the DNA60625-1507 sequence encodes a novel factor designated herein as PRO1158. However, using WU-BLAST2 sequence alignment computer programs, some sequence identities with known proteins were shown.

**35 118. Full-length PRO1159 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1159. In particular, cDNA encoding a PRO1159 polypeptide has

been identified and isolated, as disclosed in further detail in the Examples below.

The DNA60627-1508 clone was isolated from a human peripheral blood granulocyte tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA60627-1508 clone does encode a secreted factor. As far as is known, the DNA60627-1508 sequence encodes a novel factor designated herein as PRO1159; using the WU-BLAST2 sequence alignment computer program, no  
5 sequence identities to any known proteins were revealed.

#### 119. Full-length PRO1124 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1124. In particular, cDNA encoding a PRO1124 polypeptide has  
10 been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1124 (shown in Figure 274 and SEQ ID NO:377) has amino acid sequence identity with an epithelial chloride channel protein from bos taurus. PRO1124 also has sequence identity with ECAM-1. Accordingly, it is presently believed that PRO1124 disclosed in the present application is a newly identified cell  
15 membrane protein involved in communication of cells either through ion channels or cell adhesion molecules.

#### 120. Full-length PRO1287 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1287. In particular, cDNA encoding a PRO1287 polypeptide has  
20 been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1287 (shown in Figure 276 and SEQ ID NO:381) has amino acid sequence identity with the radical fringe protein from Gallus gallus (GGU82088\_1). Accordingly, it is presently believed that PRO1287 disclosed in the present application is a newly identified fringe protein homolog and may possess activity typical  
25 of the fringe protein.

#### 121. Full-length PRO1312 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1312. In particular, cDNA encoding a PRO1312 polypeptide has  
30 been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, some sequence identities with known proteins were revealed, but were determined not to be significant. Therefore, as far as is known, the DNA61873-1574 sequence encodes a novel transmembrane protein designated herein as PRO1312.

#### 35 122. Full-length PRO1192 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1192. In particular, cDNA encoding a PRO1192 polypeptide has

been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1192 (shown in Figure 280 and SEQ ID NO:389) has amino acid sequence identity with trout P0-like glycoprotein (GEN12838 IP1). Accordingly, it is presently believed that PRO1192 disclosed in the present application is a newly identified member of the myelin P0 glycoprotein family.

5

**123. Full-length PRO1160 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1160. In particular, cDNA encoding a PRO1160 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

10

The DNA62872-1509 clone was isolated from a human breast tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA62872-1509 clone does encode a secreted factor. As far as is known, the DNA62872-1509 sequence encodes a novel factor designated herein as PRO1160; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

15

**124. Full-length PRO1187 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1187. In particular, cDNA encoding a PRO1187 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

20

As far as is known, the DNA62876-1517 sequence encodes a novel factor designated herein as PRO1187; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed.

**125. Full-length PRO1185 Polypeptides**

25

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1185. In particular, cDNA encoding a PRO1185 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

As far as is known, the DNA62881-1515 clone encodes a novel factor designated herein as PRO1185; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed.

30

**126. Full-length PRO1345 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1345. In particular, cDNA encoding a PRO1345 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

35

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1345 (shown in Figure 288 and SEQ ID NO:403) has amino acid sequence identity with

the C-type lectin homolog precursor protein of bos taurus (BTU22298\_1). Accordingly, it is presently believed that PRO1345 disclosed in the present application is a newly identified member of the C-type lectin protein family and may possess activity typical of that family or of the tetranectin protein in particular.

**127. Full-length PRO1245 Polypeptides**

5 The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1245. In particular, cDNA encoding a PRO1245 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA64884-1527 clone was identified using methods that selects for nucleotide sequences encoding secreted proteins. As far as is known, the DNA64884-1527 sequence encodes a novel secreted factor designated  
10 herein as PRO1245. Using WU-BLAST2 sequence alignment computer programs, some sequence identities to known proteins were revealed; however, it was determined that they were not significant.

**128. Full-length PRO1358 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides  
15 referred to in the present application as PRO1358. In particular, cDNA encoding a PRO1358 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1358 (shown in Figure 292 and SEQ ID NO:410) has amino acid sequence identity with RASP-1. Accordingly, it is presently believed that PRO1358 disclosed in the present application is a newly identified  
20 member of the serpin family of serine protease inhibitors and may possess serine protease inhibition activity, protein catabolism inhibitory activity and/or be associated with regeneration of tissue.

**129. Full-length PRO1195 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides  
25 referred to in the present application as PRO1195. In particular, cDNA encoding a PRO1195 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1195 (shown in Figure 294 and SEQ ID NO:412) has amino acid sequence identity with MMU28486\_1, termed a proline rich acidic protein from Mus musculus, locus MMU28486, Accession:  
30 U28486, database GBTRANS, submitted 06-JUN-1995 by John W. Kasik. Accordingly, it is presently believed that PRO1195 disclosed in the present application is a newly identified member of this protein family.

**130. Full-length PRO1270 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides  
35 referred to in the present application as PRO1270. In particular, cDNA encoding a PRO1270 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.



Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1270 (shown in Figure 296 and SEQ ID NO:414) has amino acid sequence identity with the lectin protein (XLU86699\_1) of *Xenopus laevis*. Accordingly, it is presently believed that PRO1270 disclosed in the present application is a newly identified member of the lectin protein family and may possess activity typical of that family.

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### **131. Full-length PRO1271 Polypeptides**

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1271. In particular, cDNA encoding a PRO1271 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

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As far as is known, the DNA66309-1538 sequence encodes a novel factor designated herein as PRO1271; using WU-BLAST2 sequence alignment computer programs, no significant sequence identities to any known proteins were revealed (results further described in the examples below).

### **132. Full-length PRO1375 Polypeptides**

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1375. In particular, cDNA encoding a PRO1375 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1375 (shown in Figure 300 and SEQ ID NO:418) has amino acid sequence identity PUT2.

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Accordingly, it is presently believed that PRO1375 disclosed in the present application has at least one related mechanism of PUT2.

### **133. Full-length PRO1385 Polypeptides**

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1385. In particular, cDNA encoding a PRO1385 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

The DNA68869-1610 clone was isolated from a human tissue library using a trapping technique which selects for nucleotide sequences encoding secreted proteins. Thus, the DNA68869-1610 clone does encode a secreted factor. As far as is known, the DNA68869-1610 sequence encodes a novel factor designated herein as

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PRO1385; using the WU-BLAST2 sequence alignment computer program, no significant sequence identities to any known proteins were revealed.

### **134. Full-length PRO1387 Polypeptides**

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The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1387. In particular, cDNA encoding a PRO1387 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

Using the WU-BLAST2 sequence alignment computer program, it has been found that a full-length native sequence PRO1387 (shown in Figure 304 and SEQ ID NO:422) has amino acid sequence identity with the myelin p0 protein precursor (MYP0\_HETFR). Accordingly, it is presently believed that PRO1387 disclosed in the present application is a newly identified member of the myelin protein family and may possess activity typical of that family.

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### 135. Full-length PRO1384 Polypeptides

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO1384. In particular, cDNA encoding a PRO1384 polypeptide has been identified and isolated, as disclosed in further detail in the Examples below.

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Using WU-BLAST2 sequence alignment computer programs, it has been found that a full-length native sequence PRO1384 (shown in Figure 306 and SEQ ID NO:424) has amino acid sequence identity with NKG2-D (AF054819\_1; Dayhoff database, version 35.45 SwissProt 35). Accordingly, it is presently believed that PRO1384 disclosed in the present application is a newly identified member of the NKG2 family and may possess MHC activation/inactivation activities typical of the NKG2 family.

15

### B. PRO Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

20

Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

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PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein.

Certain fragments lack amino acid residues that are not essential for a desired biological activity of the PRO polypeptide.

5 PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed  
10 herein.

In particular embodiments, conservative substitutions of interest are shown in Table 1 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 1, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 1

	<u>Original Residue</u>	<u>Exemplary Substitutions</u>	<u>Preferred Substitutions</u>
5	Ala (A)	val; leu; ile	val
	Arg (R)	lys; gln; asn	lys
	Asn (N)	gln; his; lys; arg	gln
	Asp (D)	glu	glu
	Cys (C)	ser	ser
10	Gln (Q)	asn	asn
	Glu (E)	asp	asp
	Gly (G)	pro; ala	ala
	His (H)	asn; gln; lys; arg	arg
	Ile (I)	leu; val; met; ala; phe;	
15		norleucine	leu
	Leu (L)	norleucine; ile; val;	
		met; ala; phe	ile
	Lys (K)	arg; gln; asn	arg
	Met (M)	leu; phe; ile	leu
20	Phe (F)	leu; val; ile; ala; tyr	leu
	Pro (P)	ala	ala
	Ser (S)	thr	thr
	Thr (T)	ser	ser
	Trp (W)	tyr; phe	tyr
25	Tyr (Y)	trp; phe; thr; ser	phe
	Val (V)	ile; leu; met; phe;	
		ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gln, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl. Acids Res., 13:4331 (1986); Zoller et al., Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells et al., Gene, 34:315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant



DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

### 10 C. Modifications of PRO

Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO. Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimide.

20 Other modifications include deamidation of glutamyl and asparagyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the  $\alpha$ -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

25 Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

30 Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, 255:192-194 (1992)]; an  $\alpha$ -tubulin epitope peptide [Skinner et al., J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

#### D. Preparation of PRO

The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., 85:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

##### 1. Isolation of DNA Encoding PRO

DNA encoding PRO may be obtained from a cDNA library prepared from tissue believed to possess the PRO mRNA and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like <sup>32</sup>P-labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example,  $\text{CaCl}_2$ ,  $\text{CaPO}_4$ , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. Bact., 130:946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., Methods in Enzymology, 185:527-537 (1990) and Mansour et al., Nature, 336:348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA* ; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7*



*ilvG kan<sup>r</sup>*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., Bio/Technology, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., J. Bacteriol., 737 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickerhamii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilum* (ATCC 36,906; Van den Berg et al., Bio/Technology, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., J. Basic Microbiol., 28:265-278 [1988]); *Candida*; *Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case et al., Proc. Natl. Acad. Sci. USA, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., Biochem. Biophys. Res. Commun., 112:284-289 [1983]; Tilburn et al., Gene, 26:205-221 [1983]; Yelton et al., Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4:475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

### 3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally

include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

5 The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g.,  
10 the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces*  $\alpha$ -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral  
15 secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 $\mu$  plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for  
20 cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

25 An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature,  
30 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well  
35 known. Promoters suitable for use with prokaryotic hosts include the  $\beta$ -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid

promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding PRO.

5 Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

10 Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

15 PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

20 Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin,  $\alpha$ -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the PRO coding sequence, but is preferably located at a site 5' from the promoter.

25 Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding PRO.

30 Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant vertebrate cell culture are described in Gething et al., Nature, 293:620-625 (1981); Mantei et al., Nature, 281:40-46 (1979); EP 117,060; and EP 117,058.

#### 4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

#### 5. Purification of Polypeptide

Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

#### E. Uses for PRO

Nucleotide sequences (or their complement) encoding PRO have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.



The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO mRNA (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48:2659, 1988) and van der Krol et al. (BioTechniques 6:958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example,  $\text{CaPO}_4$ -mediated DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral  
5 vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable  
10 ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target  
15 nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO coding sequences.

Nucleotide sequences encoding a PRO can also be used to construct hybridization probes for mapping  
20 the gene which encodes that PRO and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO encode a protein which binds to another protein (example, where  
25 the PRO is a receptor), the PRO can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO can be used to isolate correlative ligand(s). Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO or  
30 a receptor for PRO. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

35 Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene,

which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a PRO "knock out" animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the PRO polypeptide.

Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA.



Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik *et al.*, Proc. Natl. Acad. Sci. USA 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau *et al.*, Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem. 262, 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson *et al.*, Science 256, 808-813 (1992).

The PRO polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes.

The nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO polypeptides and nucleic acid molecules of the present invention may also be used for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another. PRO nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the



dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™, PLURONICS™ or PEG.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e.g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The use of interspecies scaling in toxicokinetics" In *Toxicokinetics and New Drug Development*, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When *in vivo* administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about 1 µg/kg/day to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature; see, for example, U.S. Pat. Nos. 4,657,760; 5,206,344; or 5,225,212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- (rhIFN- ), interleukin-2, and MN rgp120. Johnson et al., *Nat. Med.*, 2:795-799 (1996); Yasuda, *Biomed. Ther.*, 27:1221-1223 (1993); Hora et al., *Bio/Technology*, 8:755-758 (1990); Cleland, "Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems," in *Vaccine Design: The Subunit and Adjuvant Approach*, Powell and Newman, eds, (Plenum Press: New York, 1995), pp. 439-462; WO 97/03692, WO 96/40072, WO 96/07399; and U.S. Pat. No. 5,654,010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of PLGA, lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer," in: M. Chasin and  
5 R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker: New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptides  
10 encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

15 All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the  
20 drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized  
25 component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody  
30 specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-  
35 protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many

transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for  $\beta$ -galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a



single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiationsite, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.



Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Rossi, Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

5 Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

10 These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

PRO189 can be used in assays with W01A6.1 of *C. Elegans*, phosphodiesterases, transporters and proteins which bind to fatty acids, to determine the relative activities of PRO189 against these proteins. The results can be applied accordingly.

15 F. Anti-PRO Antibodies

The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

20 1. Polyclonal Antibodies

The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

30 The immunization protocol may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975).

35 In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103].

5   Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will  
10   include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk  
15   Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of  
20   monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

25   After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra]. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture  
30   medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding  
35   specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells,

or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., *supra*] or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

*In vitro* methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

### 3. Human and Humanized Antibodies

The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')<sub>2</sub> or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers

[Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. Biol., 227:381 (1991); Marks et al., J. Mol. Biol., 222:581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 147(1):86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology 10, 779-783 (1992); Lonberg *et al.*, Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild *et al.*, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

#### 4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities [Milstein and Cuello, Nature, 305:537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in



at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. F(ab')<sub>2</sub> bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al.*, Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')<sub>2</sub> fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab' fragments may be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby *et al.*, J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')<sub>2</sub> molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al.*, J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al.*, Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V<sub>H</sub>) connected to a light-chain variable domain (V<sub>L</sub>) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V<sub>H</sub> and V<sub>L</sub> domains of one fragment are forced to pair with

the complementary  $V_L$  and  $V_H$  domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber *et al.*, J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al.*, J. Immunol. 147:60 (1991).

5 Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein. Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize  
10 cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

#### 15 5. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro*  
20 using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

#### 25 6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased  
30 complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron *et al.*, J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.* Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).  
35

## 7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above.

5 Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are  
10 available for the production of radioconjugated antibodies. Examples include  $^{212}\text{Bi}$ ,  $^{131}\text{I}$ ,  $^{131}\text{In}$ ,  $^{90}\text{Y}$ , and  $^{186}\text{Re}$ .

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-  
15 diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, **238**: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

20 In another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

## 8. Immunoliposomes

25 The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, **82**: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, **77**: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No.  
30 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin  
35 *et al.*, J. Biol. Chem., **257**: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See Gabizon *et al.*, J. National Cancer Inst., **81**(19): 1484 (1989).



## 9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, *e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and  $\gamma$  ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT<sup>TM</sup> (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.



### G. Uses for anti-PRO Antibodies

The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, *e.g.*, detecting its expression in specific cells, tissues, or serum. Various diagnostic assay techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases  
5 [Zola, Monoclonal Antibodies: A Manual of Techniques, CRC Press, Inc. (1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such as  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , or  $^{125}\text{I}$ , a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or  
10 horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144:945 (1962); David et al., Biochemistry, 13:1014 (1974); Pain et al., J. Immunol. Meth., 40:219 (1981); and Nygren, J. Histochem. and Cytochem., 30:407 (1982).

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture  
15 or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the  
20 antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

### EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas,  
30 VA.

#### EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about  
35 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (*e.g.*, Dayhoff, GenBank), and proprietary databases (*e.g.* LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program WU-BLAST-2

(Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

5 Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of WU-BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

10 Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per 15 Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized 20 appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

#### EXAMPLE 2: Isolation of cDNA clones by Amylase Screening

##### 25 1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linked cDNA 30 was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

##### 2. Preparation of random primed cDNA library

35 A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA

was sized to 500-1000 bp, linked with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

### 3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e.g. CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, *ura3-52*, *leu2-3*, *leu2-112*, *his3-11*, *his3-15*, *MAL<sup>+</sup>*, *SUC<sup>+</sup>*, *GAL<sup>+</sup>*. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec71*, *sec72*, *sec62*, with truncated *sec71* being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e.g., SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et al., Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about  $2 \times 10^6$  cells/ml (approx.  $OD_{600}=0.1$ ) into fresh YEPD broth (500 ml) and regrown to  $1 \times 10^7$  cells/ml (approx.  $OD_{600}=0.4-0.5$ ).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM  $Li_2OOCCH_3$ ), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100  $\mu$ l) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1  $\mu$ g, vol. < 10  $\mu$ l) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600  $\mu$ l, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li<sub>2</sub>OOCCH<sub>3</sub>, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500  $\mu$ l, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200  $\mu$ l) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et al., Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et al., Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

#### 4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30  $\mu$ l) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5  $\mu$ l) was used as a template for the PCR reaction in a 25  $\mu$ l volume containing: 0.5  $\mu$ l Klentaq (Clontech, Palo Alto, CA); 4.0  $\mu$ l 10 mM dNTP's (Perkin Elmer-Cetus); 2.5  $\mu$ l Kentaq buffer (Clontech); 0.25  $\mu$ l forward oligo 1; 0.25  $\mu$ l reverse oligo 2; 12.5  $\mu$ l distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:3)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:4)

PCR was then performed as follows:

- a. Denature 92°C, 5 minutes
- b. 3 cycles of: Denature 92°C, 30 seconds



		Anneal	59°C,	30 seconds
		Extend	72°C,	60 seconds
5	c.	3 cycles of:		
		Denature	92°C,	30 seconds
		Anneal	57°C,	30 seconds
		Extend	72°C,	60 seconds
10	d.	25 cycles of:		
		Denature	92°C,	30 seconds
		Anneal	55°C,	30 seconds
		Extend	72°C,	60 seconds
	e.	Hold	4°C	

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5  $\mu$ l) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et al., supra. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

#### EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e.g., GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

#### EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO281

In order to obtain a cDNA clone encoding PRO281, methods described in Klein et al., Proc. Natl. Acad. Sci. USA 93:7108-7113 (1996) were employed with the following modifications. Yeast transformation was performed with limiting amounts of transforming DNA in order to reduce the number of multiple transformed yeast cells. Instead of plasmid isolation from the yeast followed by transformation of *E. coli* as

described in Klein et al., *supra*, PCR analysis was performed on single yeast colonies. PCR primers employed were bipartite in order to amplify the insert and a small portion of the invertase gene (allowing to determine that the insert was in frame with invertase) and to add on universal sequencing primer sites.

5 An invertase library was transformed into yeast and positives were selected on sucrose plates. Positive clones were re-tested and PCR products were sequenced. The sequence of one clone, PRO281, was determined to contain a signal peptide coding sequence. Oligonucleotide primers and probes were designed using the nucleotide sequence of PRO281. A full length plasmid library of cDNAs from human umbilical vein endothelium tissue was titered and approximately 100,000 cfu were plated in 192 pools of 500 cfu/pool into 96-well round bottom plates. The plates were sealed and pools were grown overnight at 37°C with shaking (200rpm). PCR was performed on the individual cultures using primers. Agarose gel electrophoresis was performed and positive wells were identified by visualization of a band of the expected size. Individual positive clones were obtained by colony lift followed by hybridization with <sup>32</sup>P-labeled oligonucleotide. These clones were characterized by PCR, restriction digest, and southern blot analyses.

15 A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 80-82, and a stop signal at nucleotide positions 1115-1117 (Figure 1, SEQ ID NO:1). The predicted polypeptide precursor is 345 amino acids long, has a calculated molecular weight of approximately 37,205 daltons and an estimated pI of approximately 10.15. Analysis of the full-length PRO281 sequence shown in Figure 2 (SEQ ID NO:2) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 14, multiple transmembrane domains from about amino acid position 83 to about amino acid position 105, from about amino acid position 126 to about amino acid position 146, from about amino acid position 158 to about amino acid position 177, from about amino acid position 197 to about amino acid position 216, from about amino acid position 218 to about amino acid position 238, from about amino acid position 245 to about amino acid position 265, and from about amino acid position 271 to about amino acid position 290 and an amino acid sequence block having homology to G-protein coupled receptor proteins from about amino acid 115 to about amino acid 155. Clone UNQ244 (DNA16422-1209) has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209929.

25 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 2 (SEQ ID NO:2), evidenced significant homology between the PRO281 amino acid sequence and the following Dayhoff sequences: H64634, AF033095\_1, B64815, YBHL\_ECOLI, EMEQUTR\_1, AF064763\_3, S53708, A69253, AF035413\_12 and S63281.

#### EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO276

35 In order to obtain a cDNA clone encoding PRO276, methods described in Klein et al., *PNAS*, 93:7108-7113 (1996) were employed with the following modifications. Yeast transformation was performed with limiting amounts of transforming DNA in order to reduce the number of multiple transformed yeast cells. Instead of plasmid isolation from the yeast followed by transformation of *E. coli* as described in Klein et al., *supra*, PCR analysis was performed on single yeast colonies. PCR primers employed were bipartite in order to amplify the

insert and a small portion of the invertase gene (allowing to determine that the insert was in frame with invertase) and to add on universal sequencing primer sites.

An invertase library was transformed into yeast and positives were selected on sucrose plates. Positive clones were re-tested and PCR products were sequenced. The sequence of one clone, PRO276, was determined to contain a signal peptide coding sequence. Oligonucleotide primers and probes were designed using the nucleotide sequence of PRO276. A full length plasmid library of cDNAs from human fetal liver cells was titred and approximately 100,000 cfu were plated in 192 pools of 500 cfu/pool into 96-well round bottom plates. The plates were sealed and pools were grown overnight at 37 C with shaking (200rpm). PCR was performed on the individual cultures using primers. Agarose gel electrophoresis was performed and positive wells were identified by visualization of a band of the expected size. Individual positive clones were obtained by colony lift followed by hybridization with <sup>32</sup>P-labeled oligonucleotide. These clones were characterized by PCR, restriction digest, and southern blot analyses.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 180-182 and a stop signal at nucleotide positions 933-935 (Figure 3; SEQ ID NO:5). The predicted polypeptide precursor is 251 amino acids long has a calculated molecular weight of approximately 28,801 daltons and an estimated pI of approximately 9.58. The transmembrane domains are approximately at amino acids 98-116 and 152-172 of the sequence shown in Figure 4 (SEQ ID NO:6). Clone DNA16435-1208 (UNQ243) has been deposited with the ATCC and is assigned ATCC deposit no. 209930.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 4 (SEQ ID NO:6), revealed some sequence identity between the PRO276 amino acid sequence and the following Dayhoff sequences: CEG25D7\_2, ATT8O5\_2, S69696, GRHR\_RAT, NPCBAABCD\_3, AB013149\_1, P\_R85942 and AP000006\_5.

#### EXAMPLE 6: Isolation of cDNA clones Encoding Human PRO189

A clone designated herein as DNA14187 was isolated as described in Example 2 above from a human retina tissue library. The DNA14187 sequence is shown in Figure 7 (SEQ ID NO:9). Based on the DNA14187 sequence shown in Figure 7 (SEQ ID NO:9), oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO189. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer      5'-TTGACCTATACAGAGATTCATC-3' (SEQ ID NO:10); and  
reverse PCR primer      5'-CTAAGAACTTCCCTCAGGATTTT-3' (SEQ ID NO:11).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA14187 sequence which had the following nucleotide sequence:

hybridization probe

5'-ATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGC-3' (SEQ ID NO:12).

5 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO189 gene using the probe oligonucleotide and one of the PCR primers.

10 RNA for construction of the cDNA libraries was isolated from human retina tissue (LIB94). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

15 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO189 and the derived protein sequence for PRO189.

The entire nucleotide sequence of DNA21624-1391 is shown in Figure 5 (SEQ ID NO:7). Clone DNA21624-1391 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 200-202 and ending at the stop codon at nucleotide positions 1301-1303 (Figure 5). The predicted polypeptide precursor is 367 amino acids long (Figure 6). The full-length PRO189 protein shown in Figure 6  
20 has an estimated molecular weight of about 41,871 daltons and a pI of about 5.06. Clone DNA21624-1391 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analyzing the amino acid sequence of SEQ ID NO:8, the putative N-glycosylation sites are at about amino acids 224-227, 246-249 and 285-288. A domain for cytosolic fatty-acid binding proteins is at amino acids  
25 78-107 of SEQ ID NO:8. The corresponding nucleotides can be routinely determined given the sequences provided herein.

Some sequence identity was found to W01A6.1 and F35D11.11, C. Elegans proteins, designated in a Dayhoff database as CEW01A6\_10 and CELF35D11\_11, respectively. Some sequence identity was also found to an antigen to malaria and to restin, designated in a Dayhoff database as P\_R05766 and AF014012\_1,  
30 respectively. Some sequence identity was also found to a microtubule binding protein and to myosin, designated in a Dayhoff database as AF041382\_1 and S07537, respectively. There is also some sequence identity with 1-phosphatidylinositol-4, 5-bisphosphate, designated as PIP1\_RAT.

EXAMPLE 7: Isolation of cDNA clones Encoding Human PRO190

35 A clone designated herein as DNA14232 was isolated as described in Example 2 above from a human fetal retina tissue library. The DNA14232 sequence is shown in Figure 10 (SEQ ID NO:15). Based on the DNA14232 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained



the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO190. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

A pair of PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTATACCTACTGTAGCTTCT-3' (SEQ ID NO:16); and

reverse PCR primer 5'-TCAGAGAATTCCTTCCAGGA-3' (SEQ ID NO:17).

10 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA14232 sequence which had the following nucleotide sequence:

hybridization probe

5'-ACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCACA-3' (SEQ ID NO:18).

15 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO190 gene using the probe oligonucleotide and one of the PCR primers:

RNA for construction of the cDNA libraries was isolated from human retina tissue (LIB94). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to Sall hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

25 DNA sequencing of the clones isolated as described above gave sequences which include the full-length DNA sequence for PRO190 [herein designated as DNA23334-1392] (SEQ ID NO:13) and the derived protein sequence for PRO190.

The entire nucleotide sequence of DNA23334-1392 is shown in Figure 8 (SEQ ID NO:13). Clone DNA23334-1392 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 193-195 and which ends at the stop codon at nucleotide positions 1465-1467 (Figure 8). The predicted polypeptide precursor is 424 amino acids long (Figure 9). The full-length PRO190 protein shown in Figure 9 has an estimated molecular weight of about 48,500 daltons and a pI of about 8.65. Clone DNA23334-1392 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

35 Analyzing the amino acid sequence of SEQ ID NO:14, the putative transmembrane domains are at about amino acids 16-36, 50-74, 147-168, 229-250, 271-293, 298-318 and 328-368 of SEQ ID NO:14. N-glycosylation sites are at about amino acids 128-131, 204-207, 218-221 and 274-377 of SEQ ID NO:14. The corresponding nucleotides can be routinely determined given the sequences provided herein.

PRO190 has sequence identity with at least the following Dayhoff sequences designated as: CEZK896\_2, JC5023, GMS1\_SCHPO and S44668.

**EXAMPLE 8: Isolation of cDNA clones Encoding Human PRO341**

5 A clone designated herein as DNA12920 was isolated as described in Example 2 above from a human placenta tissue library. The DNA12920 sequence is shown in Figure 13 (SEQ ID NO:21). The DNA12920 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in  
10 some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA25314. Oligonucleotide primers based upon the DNA25314 sequence were then synthesized and employed to screen a human placenta cDNA library which resulted in the identification of the DNA26288-1239 clone shown in Figure 11. The cloning vector was pRK5B (pRK5B is a  
15 precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 380-382, and a stop signal at nucleotide positions 1754-1756 (Figure 11, SEQ ID NO:19). The predicted polypeptide precursor is 458 amino acids long, has a calculated  
20 molecular weight of approximately 50,264 daltons and an estimated pI of approximately 8.17. Analysis of the full-length PRO341 sequence shown in Figure 12 (SEQ ID NO:20) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 17, transmembrane domains from about amino acid 171 to about amino acid 190, from about amino acid 220 to about amino acid 239, from about amino acid 259 to about amino acid 275, from about amino acid 286 to about amino acid 305, from about amino acid 316 to  
25 about amino acid 335, from about amino acid 353 to about amino acid 378 and from about amino acid 396 to about amino acid 417 and potential N-glycosylation sites from about amino acid 145 to about amino acid 147 and from about amino acid 155 to about amino acid 158. Clone DNA26288-1239 has been deposited with ATCC on April 21, 1998 and is assigned ATCC deposit no. 209792.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence  
30 alignment analysis of the full-length sequence shown in Figure 12 (SEQ ID NO:20), evidenced homology between the PRO341 amino acid sequence and the following Dayhoff sequences: S75696, H69788, D69852, A69888, B64918, F64752, LPU89276\_1, G64962, S52977 and S44253.

**EXAMPLE 9: Isolation of cDNA clones Encoding Human PRO180**

35 A clone designated herein as DNA12922 was isolated as described in Example 2 above from a human placenta tissue library. The DNA12922 sequence is shown in Figure 16 (SEQ ID NO:24). The DNA12922 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a

proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

5 An oligonucleotide probe was formed based upon the consensus sequence obtained above. This probe had the following sequence.

5'-ACCTGTTAGAAATGTGGTGGTTTCAGCAAGGCCTCAGTTT (SEQ ID NO:25).

This probe was used to screen a human placenta library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, 10 Holmes et al., Science, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp. A clone designated herein as DNA26843-1389 was obtained.

The entire nucleotide sequence of DNA26843-1389 is shown in Figure 14 (SEQ ID NO:22). Clone DNA26843-1389 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and ending at the stop codon at nucleotide positions 919-921 (Figure 14). The predicted 15 polypeptide precursor is 266 amino acids long (Figure 15). The full-length PRO180 protein shown in Figure 15 has an estimated molecular weight of about 29,766 daltons and a pI of about 8.39. Clone DNA26843-1389 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

20 Still analyzing the amino acid sequence of SEQ ID NO:23, the transmembrane domains are at about amino acids 13-33 (type II), 54-73, 94-113, 160-180 and 122-141 of SEQ ID NO:23. N-myristoylation sites are at about amino acids 57-62, 95-100, 99-104, 124-129 and 183-188 of SEQ ID NO:23. The corresponding nucleotides can be routinely determined given the sequences provided herein.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 15 (SEQ ID NO:23), evidenced some sequence 25 identity between the PRO180 amino acid sequence and the following Dayhoff sequences: CEC33A11\_2, CEG11E6\_5, CELW03A5\_1 AND PEU83861\_2 (NADH dehydrogenase subunit 4L, mitochondrion).

#### EXAMPLE 10: Isolation of cDNA clones Encoding Human PRO194

30 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein DNA19464. Based on the DNA19464 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO194. PCR primers (forward and reverse) were synthesized based upon the DNA19464 sequence. Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA19464 sequence.

35 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO194 gene using the probe oligonucleotide and one of the PCR primers. RNA



for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO194 [herein designated as DNA26844-1394] (SEQ ID NO:27) and the derived protein sequence for PRO194.

The entire nucleotide sequence of DNA26844-1394 is shown in Figure 17 (SEQ ID NO:27). Clone  
 5 DNA26844-1394 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 81-83 and ending at the stop codon at nucleotide positions 873-875 (Figure 17). The predicted polypeptide precursor is 264 amino acids long (Figure 18). The full-length PRO194 protein shown in Figure 18 has an estimated molecular weight of about 29,665 daltons and a pI of about 9.34. Analysis of the full-length PRO194 sequence shown in Figure 18 (SEQ ID NO:28) evidences the presence of various important  
 10 polypeptides domains as shown in Figure 18. Clone DNA26844-1394 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209926.

Analysis of the amino acid sequence of the full-length PRO194 polypeptide suggests that it does not exhibit significant sequence similarity to any known human protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some homology between the PRO194 amino acid sequence and  
 15 the following Dayhoff sequences, HUMORFT\_1, CET07F10\_5, ATFCA9\_12, F64934, YDJX\_ECOLI, ATAF00065719F29G20.19, H70002, S76980, H64934 and S76385.

#### EXAMPLE 11: Isolation of cDNA clones Encoding Human PRO203

A clone designated herein as DNA15618 was isolated as described in Example 2 above from a human  
 20 fetal lung tissue library. The DNA15618 sequence is shown in Figure 21 (SEQ ID NO:31). Oligonucleotide probes were generated from the sequence of the DNA15618 molecule and were used to screen a human fetal lung library (LIB26) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 159-161 and ending at the stop codon found at nucleotide positions 1200-1202 (Figure 19; SEQ ID NO:29). The predicted polypeptide precursor is 347 amino acids long, has a calculated molecular weight of approximately 39,870 daltons and an estimated pI of approximately 6.76. Analysis of the full-length PRO203 sequence shown in Figure 20 (SEQ ID NO:30) evidences the presence of  
 30 the following: a type II transmembrane domain at about amino acid 64 to about amino acid 87; possible N-glycosylation sites at about amino acid 147 to about amino acid 150, about amino acid 155 to about amino acid 158, and about amino acid 237 to about amino acid 240; sequence identity with heavy-metal-associated domain proteins at about amino acid 23 to about amino acid 45, and sequence identity with D-isomer specific 2-hydroxyacid dehydrogenase at about amino acid 24 to about amino acid 34. Clone DNA30862-1396 was  
 35 deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209920.

Analysis of the amino acid sequence of the full-length PRO203 polypeptide suggests that it possesses sequence similarity to GST ATPase, thereby indicating that PRO203 may be a novel GST ATPase. More



specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO203 amino acid sequence and the following Dayhoff sequences, AF008124\_1, CFRCD1GEN\_1, and P\_R82566.

#### EXAMPLE 12: Isolation of cDNA clones Encoding Human PRO290

5 An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified that had homology to beige and FAN. An oligonucleotide probe based upon the identified EST sequence was then synthesized and used to screen human fetal kidney cDNA libraries in an attempt to identify a full-length cDNA clone. The oligonucleotide probe had the following sequence:

5' TGACTGCACTACCCCGTGGCAAGCTGTTGAGCCAGCTCAGCTG 3' (SEQ ID NO:34).

10 RNA for construction of cDNA libraries was isolated from human fetal kidney tissue. The cDNA libraries used to isolate the cDNA clones encoding human PRO290 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as  
15 pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science* 253:1278-1280 (1991)) in the unique XhoI and NotI.

A cDNA clone was identified and sequenced in entirety. The entire nucleotide sequence of DNA35680-1212 is shown in Figure 22 (SEQ ID NO:32). Clone DNA35680-1212 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 293-295, and a stop codon at nucleotide positions  
20 3302-3304 (Figure 22; SEQ ID NO:32). The predicted polypeptide precursor is 1003 amino acids long.

It is currently believed that the PRO290 polypeptide is related to FAN and/or beige. Clone DNA35680-1212 has been deposited with ATCC and is assigned ATCC deposit no. 209790. It is understood that the deposited clone has the actual correct sequence rather than the representations provided herein. The full-length PRO290 protein shown in Figure 23 has an estimated molecular weight of about 112,013 daltons and a pI of  
25 about 6.4.

#### EXAMPLE 13: Isolation of cDNA Clones Encoding Human PRO874

A consensus DNA sequence designated herein as DNA36459 was identified using phrap as described in Example 1 above. Based on the DNA36459 consensus sequence, oligonucleotides were synthesized: 1) to  
30 identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the coding sequence for PRO874.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TCGTGCCCAGGGGCTGATGTGC-3' (SEQ ID NO:37); and

reverse PCR primer 5'-GTCTTTACCCAGCCCCGGGATGCG-3' (SEQ ID NO:38).

35 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36459 sequence which had the following nucleotide sequence:

hybridization probe

5'-GGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCCTGGG-3' (SEQ ID NO:39).

In order to screen several libraries for a source of a clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO874 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the DNA sequence for PRO874 [herein designated as DNA40621-1440] (SEQ ID NO:35) and the derived protein sequence for PRO874.

The entire nucleotide sequence of DNA40621-1440 is shown in Figure 24 (SEQ ID NO:35). Clone DNA40621-1440 contains a single open reading frame ending at the stop codon at nucleotide positions 964-966 (Figure 24). The predicted polypeptide encoded by DNA40621-1440 is 321 amino acids long (Figure 25). The PRO874 protein shown in Figure 25 has an estimated molecular weight of about 36,194 daltons and a pI of about 9.85. Analysis of the PRO874 sequence shown in Figure 25 (SEQ ID NO:36) evidenced the presence of the following: a type II transmembrane domain at about amino acids 57-80; additional transmembrane domains at about amino acids 110-126, 215-231, and 254-274; potential N-glycosylation sites at about amino acids 16-19, 27-30, and 289-292; sequence identity with hypothetical YBR002c family proteins at about amino acids 276-287; and sequence identity with ammonium transporter proteins at about amino acids 204-230. Clone DNA40621-1440 was deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209922.

Analysis of the amino acid sequence of the PRO874 polypeptide suggests that it is a novel multi-span transmembrane protein. However, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO874 amino acid sequence and the following Dayhoff sequences: S67049, AF054839\_1, S73437, S52460, and HIVU80570\_1.

EXAMPLE 14: Isolation of cDNA Clones Encoding Human PRO710

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone whose sequence (herein designated as DNA38190) is shown in Figure 28 (SEQ ID NO:42). Based on the DNA38190 sequence shown in Figure 28, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO710. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TTCCGCAAAGAGTTCTACGAGGTGG-3' (SEQ ID NO:43)

reverse PCR primer 5'-ATTGACAACATTGACTGGCCTATGGG-3' (SEQ ID NO:44)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA38190 sequence which had the following nucleotide sequence

hybridization probe

5'-GTGGATGCTCTGTGTGCGTGCAAGATCCTTCAGGCCTTGTTCCAGTGTGA-3' (SEQ ID NO:45)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO710 gene using the probe oligonucleotide and one of the PCR primers.

5 RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 10 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 67-69 and ending at the stop codon found at nucleotide positions 1765-1767 (Figure 26, SEQ ID NO:40). The predicted polypeptide precursor is 566 amino acids long, has a calculated molecular weight of approximately 65,555 daltons and an estimated pI of approximately 5.44. 15 Analysis of the full-length PRO710 sequence shown in Figure 27 (SEQ ID NO:41) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 32, a transmembrane domain from about amino acid 454 to about amino acid 476, an aminoacyl-transfer RNA synthetase class-II signature sequence from about amino acid 6 to about amino acid 26 and potential N-glycosylation sites from about amino acid 111 20 to about amino acid 114, from about amino acid 146 to about amino acid 149 and from about amino acid 292 to about amino acid 295. Clone DNA44161-1434 has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209907.

Analysis of the amino acid sequence of the full-length PRO710 polypeptide suggests that it possesses significant sequence similarity to the CDC45 protein, thereby indicating that PRO710 may be a novel CDC45 25 homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO710 amino acid sequence and the following Dayhoff sequences, HSAJ3728\_1, CEF34D10\_1, S64939, UMU50276\_1, TRHY\_SHEEP, CELT14E8\_1, RNA1\_YEAST, LVU89340\_1, HSU80736\_1 and CEZK337\_2.

### 30 EXAMPLE 15: Isolation of cDNA clones Encoding Human PRO1151

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA40665. Based on the DNA40665 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for 35 PRO1151.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCAGACGCTGCTCTTCGAAAGGGTC-3' (SEQ ID NO:48)

reverse PCR primer 5'-GGTCCCCGTAGGCCAGGTCCAGC-3' (SEQ ID NO:49)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40665 sequence which had the following nucleotide sequence

5 hybridization probe

5'-CTACTTCTTCAGCCTCAATGTGCACAGCTGGAATTACAAGGAGACGTACG-3' (SEQ ID NO:50)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1151 gene using the probe oligonucleotide and one of the PCR primers. RNA  
10 for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1151 (designated herein as DNA44694-1500 [Figure 29, SEQ ID NO:46]; and the derived protein sequence for PRO1151.

The entire nucleotide sequence of DNA44694-1500 is shown in Figure 29 (SEQ ID NO:46). Clone  
15 DNA44694-1500 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 272-274 and ending at the stop codon at nucleotide positions 1049-1051 (Figure 29). The predicted polypeptide precursor is 259 amino acids long (Figure 30). The full-length PRO1151 protein shown in Figure 30 has an estimated molecular weight of about 28,770 daltons and a pI of about 6.12. Analysis of the full-length PRO1151 sequence shown in Figure 30 (SEQ ID NO:47) evidences the presence of the following: a signal  
20 peptide from about amino acid 1 to about amino acid 20, a potential N-glycosylation site from about amino acid 72 to about amino acid 75 and amino acid sequence blocks having homology to C1q domain-containing proteins from about amino acid 144 to about amino acid 178, from about amino acid 78 to about amino acid 111 and from about amino acid 84 to about amino acid 117. Clone UNQ581 (DNA44694-1500) has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203114.

25 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 30 (SEQ ID NO:47), evidenced significant homology between the PRO1151 amino acid sequence and the following Dayhoff sequences: ACR3\_HUMAN, HP25\_TAMAS, HUMC1QB2\_1, P\_R99306, CA1F\_HUMAN, JX0369, CA24\_HUMAN, S32436, P\_R28916 and CA54\_HUMAN.

30

EXAMPLE 16: Isolation of cDNA clones Encoding Human PRO1282

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA33778. Based on the DNA33778 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained  
35 the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1282.



PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'TCTTCAGCCGCTTGCGCAACCTC3' (SEQ ID NO:53); and  
reverse PCR primer 5'TTGCTCACATCCAGCTCCTGCAGG3' (SEQ ID NO:54).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA33778 sequence which had the following nucleotide sequence:

5 hybridization probe

5'TGGATGTTGTCCAGACAACCAGCTGGAGCTGTATCCGAGGC3' (SEQ ID NO:55).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1282 gene using the probe oligonucleotide and one of the PCR primers. RNA  
 10 for construction of the cDNA libraries was isolated from human fetal liver.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1282 (designated herein as DNA45495-1550 [Figure 31, SEQ ID NO:51]; and the derived protein sequence for PRO1282.

The entire coding sequence of PRO1282 is shown in Figure 31 (SEQ ID NO:51). Clone DNA45495-  
 15 1550 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 120-122, and an apparent stop codon at nucleotide positions 2139-2141 (SEQ ID NO:51). The predicted polypeptide precursor is 673 amino acids long. The signal peptide is at about amino acids 1-23; the transmembrane domain is at about amino acids 579-599; an EGF-like domain cysteine pattern signature starts at about amino acid 430; and leucine zipper patterns start at about amino acids 197 and 269 of SEQ ID NO:52,  
 20 see Figure 32. Clone DNA45495-1550 has been deposited with the ATCC and is assigned ATCC deposit no. 203156. The full-length PRO1282 protein shown in Figure 32 has an estimated molecular weight of about 71,655 daltons and a pI of about 7.8.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 32 (SEQ ID NO:52), revealed sequence identity  
 25 between the PRO1282 amino acid sequence and the following Dayhoff sequences (data from database incorporated by reference): AB007876\_1, RNPLGPV\_1, MUSLRRP\_1, ALS\_PAPPA, AC004142\_1, ALS\_HUMAN, AB014462\_1, DMTARTAN\_1, HSCHON03\_1 and S46224.

EXAMPLE 17: Isolation of cDNA clones Encoding Human PRO358

30 Using the method described in Example 1 above, a single EST sequence was identified in the Incyte database, designated herein as INC3115949. Based on the INC3115949 EST sequence, oligonucleotides were synthesized to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for PRO358.

A pair of PCR primers (forward and reverse) were synthesized:

35 forward PCR primer 5'-TCCCACCAGGTATCATAAACTGAA-3' (SEQ ID NO:58)  
reverse PCR primer 5'-TTATAGACAATCTGTTCTCATCAGAGA-3' (SEQ ID NO:59)

A probe was also synthesized:

5'-AAAAAGCATACTTGGAATGGCCCAAGGATAGGTGTAAATG-3' (SEQ ID NO:60)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO358 gene using the probe oligonucleotide and one of the PCR primers. RNA  
5 for construction of the cDNA libraries was isolated from human bone marrow (LIB256). The cDNA libraries used to isolated the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor  
10 of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO358 (Figure 33, SEQ ID NO:56) and the derived protein sequence for PRO358 (Figures 34, SEQ ID NO:57).

The entire nucleotide sequence of the clone identified (DNA47361-1154) is shown in Figure 33 (SEQ ID NO:56). Clone DNA47361-1154 contains a single open reading frame with an apparent translational initiation site (ATG start signal) at nucleotide positions underlined in Figure 33. The predicted polypeptide precursor is 811 amino acids long, including a putative signal sequence (amino acids 1 to 19), an extracellular domain (amino acids 20 to 575, including leucine rich repeats in the region from position 55 to position 575),  
20 a putative transmembrane domain (amino acids 576 to 595). Clone DNA47361-1249 has been deposited with ATCC and is assigned ATCC deposit no. 209431.

#### EXAMPLE 18: Isolation of cDNA clones Encoding Human PRO1310

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described  
25 in Example 1 above. This consensus sequence is designated herein as DNA37164. Based on the DNA37164 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1310.

PCR primers (forward and reverse) were synthesized:

30 forward PCR primer: 5'GTTCTCAATGAGCTACCCGTCCCC3' (SEQ ID NO:63) and  
reverse PCR primer: 5'CGCGATGTAGTGGAAGCTCGGGCTC3' (SEQ ID NO:64).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47394 sequence which had the following nucleotide sequence:

hybridization probe:

35 5'ATCCGCATAAACCTCAGTCCTGGTTTGATAATGGGAGCATCTGCATGAG3' (SEQ ID NO:65).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to

isolate clones encoding the PRO1310 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1310 and the derived protein sequence for PRO1310.

The entire coding sequence of PRO1310 is shown in Figures 35A-B (SEQ ID NO:61). Clone DNA47394-1572 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 326-328, and an apparent stop codon at nucleotide positions 2594-2596 (SEQ ID NO:61). The predicted polypeptide precursor is 765 amino acids long. The signal peptide is at about amino acids 1-25 of SEQ ID NO:62. Clone DNA47394-1572 has been deposited with ATCC and is assigned ATCC deposit no. 203109. The full-length PRO1310 protein shown in Figure 36 has an estimated molecular weight of about 85,898 daltons and a pI of about 6.87.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 36 (SEQ ID NO:62), revealed sequence identity between the PRO1310 amino acid sequence and the following Dayhoff sequences: AF017639\_1, P\_W36817, JC5256, CBPH\_HUMAN, MMU23184\_1, CBPN\_HUMAN, HSU83411\_1, CEF01D4\_7, RNU62897\_1 and P\_W11851.

#### EXAMPLE 19: Isolation of cDNA Clones Encoding Human PRO698

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone whose sequence (herein designated as DNA39906) is shown in Figure 39 (SEQ ID NO:68). Based on the DNA39906 sequence shown in Figure 39, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO698. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-AGCTGTGGTCATGGTGGTGTGGTG-3' (SEQ ID NO:69)

reverse PCR primer 5'-CTACCTTGGCCATAGGTGATCCGC-3' (SEQ ID NO:70)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA39906 sequence which had the following nucleotide sequence

hybridization probe

5'-CATCAGCAAACCGTCTGTGGTTCAGCTCAACTGGAGAGGGTT-3' (SEQ ID NO:71)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO698 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human bone marrow tissue (LIB255). The cDNA

libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 14-16 and ending at the stop codon found at nucleotide positions 1544-1546 (Figure 37, SEQ ID NO:66). The predicted polypeptide precursor is 510 amino acids long, has a calculated molecular weight of approximately 57,280 daltons and an estimated pI of approximately 5.61.

Analysis of the full-length PRO698 sequence shown in Figure 38 (SEQ ID NO:67) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 20, potential N-glycosylation sites from about amino acid 72 to about amino acid 75, from about amino acid 136 to about amino acid 139, from about amino acid 193 to about amino acid 196, from about amino acid 253 to about amino acid 256, from about amino acid 352 to about amino acid 355 and from about amino acid 411 to about amino acid 414 an amino acid block having homology to legume lectin beta-chain proteins from about amino acid 20 to about amino acid 39 and an amino acid block having homology to the HBGF/FGF family of proteins from about amino acid 338 to about amino acid 365. Clone DNA48320-1433 has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209904.

Analysis of the amino acid sequence of the full-length PRO698 polypeptide suggests that it possesses significant sequence similarity to the olfactomedin protein, thereby indicating that PRO698 may be a novel olfactomedin homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO698 amino acid sequence and the following Dayhoff sequences, OLFM\_RANCA, I73637, AB006686S3\_1, RNU78105\_1, RNU72487\_1, P\_R98225, CELC48E7\_4, CEF11C3\_3, XLU85970\_1 and S42257.

#### EXAMPLE 20: Isolation of cDNA Clones Encoding Human PRO732

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone whose sequence (herein designated as DNA42580) is shown in Figure 45 (SEQ ID NO:77). The DNA42580 sequence was then compared to a variety of known EST sequences to identify homologies. The EST databases employed included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).



Using the above analysis, a consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is herein designated consen01. Proprietary Genentech EST sequences were employed in the consensus assembly and they are herein designated DNA20239 (Figure 42; SEQ ID NO:74), DNA38050 (Figure 43; SEQ ID NO:75) and DNA40683 (Figure 44; SEQ ID NO:76).

Based on the consen01 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO732. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-ATGTTTGTGTGGAAGTGCCCCG-3' (SEQ ID NO:78)  
 15 forward PCR primer 5'-GTCAACATGCTCCTCTGC-3' (SEQ ID NO:79)  
reverse PCR primer 5'-AATCCATTGTGCACTGCAGCTCTAGG-3' (SEQ ID NO:80)  
reverse PCR primer 5'-GAGCATGCCACCACTGGACTGAC-3' (SEQ ID NO:81)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA44143 sequence which had the following nucleotide sequence

20 hybridization probe  
 5'-GCCGATGCTGTCCTAGTGGAAACAACCTCCACTGTAAGTAGATTGATCTATGCAC-3' (SEQ ID NO:82)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO732 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB26). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 88-90 and ending at the stop codon found at nucleotide positions 1447-1449 (Figure 40, SEQ ID NO:72). The predicted polypeptide precursor is 453 amino acids long, has a calculated molecular weight of approximately 50,419 daltons and an estimated pI of approximately 5.78. Analysis of the full-length PRO732 sequence shown in Figure 41 (SEQ ID NO:73) evidences the presence of

the following: a signal peptide from about amino acid 1 to about amino acid 28, transmembrane domains from about amino acid 37 to about amino acid 57, from about amino acid 93 to about amino acid 109, from about amino acid 126 to about amino acid 148, from about amino acid 151 to about amino acid 172, from about amino acid 197 to about amino acid 215, from about amino acid 231 to about amino acid 245, from about amino acid 260 to about amino acid 279, from about amino acid 315 to about amino acid 333, from about amino acid 384 to about amino acid 403 and from about amino acid 422 to about amino acid 447, potential N-glycosylation sites from about amino acid 33 to about amino acid 36, from about amino acid 34 to about amino acid 37, from about amino acid 179 to about amino acid 183, from about amino acid 298 to about amino acid 301, from about amino acid 337 to about amino acid 340 and from about amino acid 406 to about amino acid 409, an amino acid block having homology to the MIP family of proteins from about amino acid 119 to about amino acid 149 and an amino acid block having homology to DNA/RNA non-specific endonuclease proteins from about amino acid 279 to about amino acid 286. Clone DNA48334-1435 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209924.

Analysis of the amino acid sequence of the full-length PRO732 polypeptide suggests that it possesses significant sequence similarity to the Diff33 protein, thereby indicating that PRO732 may be a novel Diff33 homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO732 amino acid sequence and the following Dayhoff sequences, HS179M20\_2, MUSTETU\_1, CER11H6\_2, RATDRP\_1, S51256, E69226, AE000869\_1, JC4120, CYB\_PARTE and P\_R50619.

## 20 EXAMPLE 21: Isolation of cDNA clones Encoding Human PRO1120

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein consen0352. The consen0352 sequence was then extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above. The extended consensus sequence is designated herein as DNA34365. Based on the DNA34365 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1120.

PCR primers (forward and reverse) were synthesized:

forward PCR primers: 5'-GAAGCCGGCTGTCTGAATC-3' (SEQ ID NO:85),  
 30 5'-GGCCAGCTATCTCCGCAG-3' (SEQ ID NO:86), 5'-AAGGGCCTGCAAGAGAAG-3' (SEQ ID NO:87),  
 5'-CACTGGGACAACGTGTGGG-3' (SEQ ID NO:88),  
 5'-CAGAGGCAACGTGGAGAG-3' (SEQ ID NO:89), and  
 5'-AAGTATTGTCATACAGTGTTTC-3' (SEQ ID NO:90);  
reverse PCR primers: 5'-TAGTACTTGGGCACGAGGTTGGAG-3' (SEQ ID NO:91), and 5'-  
 35 TCATACCAACTGCTGGTCATTGGC-3' (SEQ ID NO:92).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA34365 consensus sequence which had the following nucleotide sequence:

hybridization probe:

5'-CTCAAGCTGCTGGACACGGAGCGGCCGGTGAATCGGTTTCACTTG-3' (SEQ ID NO:93).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1120 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1120 (designated herein as DNA48606-1479 [Figures 46A-B, SEQ ID NO:83]; and the derived protein sequence for PRO1120.

The entire coding sequence of PRO1120 is shown in Figures 46A-B (SEQ ID NO:83). Clone DNA48606-1479 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 608-610 and an apparent stop codon at nucleotide positions 3209-3211. The predicted polypeptide precursor is 867 amino acids long. The full-length PRO1120 protein shown in Figure 47 has an estimated molecular weight of about 100,156 Daltons and a pI of about 9.44. Additional features of the PRO1120 polypeptide include a signal peptide at about amino acids 1-17; a sulfatase signature at about amino acids 86-98; regions of homology to sulfatases at about amino acids 87-106, 133-146, 216-229, 291-320, and 365-375; and potential N-glycosylation sites at about amino acids 65-68, 112-115, 132-135, 149-152, 171-174, 198-201, 241-245, 561-564, 608-611, 717-720, 754-757, and 764-767.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 47 (SEQ ID NO:84), revealed significant homology between the PRO1120 amino acid sequence and the following Dayhoff sequences: CELK09C4\_1, GL6S\_HUMAN, G65169, NCU89492\_1, BCU44852\_1, E64903, P\_R51355, STS\_HUMAN, GA6S\_HUMAN, and IDS\_MOUSE. Clone DNA48606-1479 was deposited with the ATCC on July 1, 1998, and is assigned ATCC deposit no. 203040.

## 25 EXAMPLE 22: Isolation of cDNA clones Encoding Human PRO537

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated as Incyte EST cluster no. 29605. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48350.

In light of an observed sequence homology between the DNA48350 consensus sequence and an EST sequence encompassed within the Merck EST clone no. R63443, the Merck EST clone R63443 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 48 and is herein designated as DNA49141-1431.

Clone DNA49141-1431 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 97-99 and ending at the stop codon at nucleotide positions 442-444 (Figure 48). The predicted polypeptide precursor is 115 amino acids long (Figure 49). The full-length PRO537 protein shown in Figure 49 has an estimated molecular weight of about 13,183 daltons and a pI of about 12.13. Analysis of the full-length PRO537 sequence shown in Figure 49 (SEQ ID NO:95) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31, a potential N-glycosylation site from about amino acid 44 to about amino acid 47, potential N-myristoylation sites from about amino acid 3 to about amino acid 8 and from about amino acid 16 to about amino acid 21 and an amino acid block having homology to multicopper oxidase proteins from about amino acid 97 to about amino acid 105. Clone DNA49141-1431 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203003.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 49 (SEQ ID NO:95), evidenced homology between the PRO537 amino acid sequence and the following Dayhoff sequences: A54523, CELF22H10\_2, FKH4\_MOUSE, OTX1\_HUMAN, URB1\_USTMA, KNOB\_PLAFN, A32895\_1, AF036332\_1, HRG\_HUMAN and HRP3\_PLAFS.

#### EXAMPLE 23: Isolation of cDNA clones Encoding Human PRO536

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as ss.clu2437.init. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48351.

In light of an observed sequence homology between the DNA48351 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H11129, the Merck EST clone H11129 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 50 and is herein designated as DNA49142-1430.

Clone DNA49142-1430 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 48-50 and ending at the stop codon at nucleotide positions 987-989 (Figure 50). The predicted polypeptide precursor is 313 amino acids long (Figure 51). The full-length PRO536 protein shown in Figure 51 has an estimated molecular weight of about 34,189 daltons and a pI of about 4.8. Analysis of the full-length PRO536 sequence shown in Figure 51 (SEQ ID NO:97) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, a potential N-glycosylation site from about amino acid 45 to about amino acid 48 and an amino acid sequence block having homology to sulfatase proteins from



about amino acid 16 to about amino acid 26. Clone DNA49142-1430 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203002.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 51 (SEQ ID NO:97), evidenced homology between the PRO536 amino acid sequence and the following Dayhoff sequences: APU46857\_1, PK2\_DICDI, H64743, F5I14\_18, CEAM\_ECOLI, GEN14267, H64965, TCU39815\_1, PSBJ\_ODOSI and P\_R06980.

**EXAMPLE 24: Isolation of cDNA clones Encoding Human PRO535**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as ss.clu12694.init. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48352. Two proprietary Genentech EST sequences were employed in the assembly are herein shown in Figures 54 and 55.

In light of an observed sequence homology between the DNA48352 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H86994, the Merck EST clone H86994 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 52 and is herein designated as DNA49143-1429.

Clone DNA49143-1429 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 78-80 and ending at the stop codon at nucleotide positions 681-683 (Figure 52). The predicted polypeptide precursor is 201 amino acids long (Figure 53). The full-length PRO535 protein shown in Figure 53 has an estimated molecular weight of about 22,180 daltons and a pI of about 9.68. Analysis of the full-length PRO535 sequence shown in Figure 53 (SEQ ID NO:99) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, a transmembrane domain from about amino acid 155 to about amino acid 174, a potential N-glycosylation site from about amino acid 196 to about amino acid 199 and FKBP-type peptidyl-prolyl cis-trans isomer signature sequences from about amino acid 62 to about amino acid 77, from about amino acid 87 to about amino acid 123 and from about amino acid 128 to about amino acid 141. Clone DNA49143-1429 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203013.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST- sequence alignment analysis of the full-length sequence shown in Figure 53 (SEQ ID NO:99), evidenced homology between the PRO535 amino acid sequence and the following Dayhoff sequences: S71237, P\_R93551, P\_R28980, S71238, FKB2\_HUMAN, CELC05C8\_1, S55383, S72485, CELC50F2\_6 and S75144.

**EXAMPLE 25: Isolation of cDNA clones Encoding Human PRO718**

A cDNA sequence isolated in the amylase screen described in Example 2 (human fetal lung library) above is herein designated DNA43512 (see Figure 62; SEQ ID NO:108). The DNA43512 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA45625. Proprietary Genentech EST sequences were employed in the assembly and are herein shown in Figures 58-61.

Based on the DNA45625 sequence, oligonucleotide probes were generated and used to screen a human fetal lung library (LIB25) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GGGTGGATGGTACTGCTGCATCC-3' (SEQ ID NO:109)

reverse PCR primer 5'-TGTTGTGCTGTGGGAAATCAGATGTG-3' (SEQ ID NO:110)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA45625 sequence which had the following nucleotide sequence:

hybridization probe

5'-GTGTCTGGAGGCTGTGGCCGTTTTGTTTTCTTGGGCTAAAATCGGG-3' (SEQ ID NO:111)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO718 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 36-38 and ending at the stop codon found at nucleotide positions 607-609 (Figure 56; SEQ ID NO:102). The predicted polypeptide precursor is 157 amino acids long, has a calculated molecular weight of approximately 17,400 daltons and an estimated pI of approximately 5.78. Analysis of the full-length PRO718 sequence shown in Figure 57 (SEQ ID NO:103) evidences the presence of the following: a type II transmembrane domain from about amino acid 21 to about amino acid 40, and other transmembrane domains at about amino acid 58 to about amino acid 78, about amino acid 95 to about amino acid 114, and about amino acid 127 to about amino acid 147; a cell attachment sequence from about amino acid 79 to about amino acid 81; and a potential N-glycosylation site from about amino acid 53 to about amino acid 56. Clone DNA49647-1398 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209919.

Analysis of the amino acid sequence of the full-length PRO718 polypeptide suggests that it possesses no significant sequence similarity to any known protein. However, an analysis of the Dayhoff database (version

35.45 SwissProt 35) evidenced some degree of homology between the PRO718 amino acid sequence and the following Dayhoff sequences: AF045606\_1, AF039906\_1, SPBC8D2\_2, S63441, F64728, COX1\_TRYBB, F64375, E64173, RPYGJT\_3, MTCY261\_23.

**EXAMPLE 26: Isolation of cDNA clones Encoding Human PRO872**

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence designated herein as clu120709.init. The clu120709.init sequence was then compared a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or  
10 in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48254.

In light of an observed sequence homology between the DNA48254 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3438068, the Incyte EST clone 3438068 was purchased  
15 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 63 and is the full-length DNA sequence for PRO872. Clone DNA49819-1439 was deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209931.

The entire nucleotide sequence of DNA49819-1439 is shown in Figure 63 (SEQ ID NO:112). Clone  
20 DNA49819-1439 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 14-16 and ending at the stop codon at nucleotide positions 1844-1846 (Figure 63). The predicted polypeptide precursor is 610 amino acids long (Figure 64). The full-length PRO872 protein shown in Figure 64 has an estimated molecular weight of about 66,820 daltons and a pI of about 8.65. Analysis of the full-length PRO872 sequence shown in Figure 64 (SEQ ID NO:113) evidences the presence of the following features: a  
25 signal peptide at amino acid 1 to about 18, putative transmembrane domains at about amino acids 70-87, 200-222 and 568-588; sequence identity with bacterial-type phytoene dehydrogenase protein at about amino acids 71-105; sequence identity with a regulator of chromosome condensation (RCC1) signature 2 at about amino acids 201-211; leucine zipper patterns at about amino acids 214-235, 221-242, 228-249 and 364-385; a potential N-glycosylation site at about amino acids 271-274; and a glycosaminoglycan attachment site at about amino acids  
30 75-78. Analysis of the amino acid sequence of the full-length PRO872 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO872 amino acid sequence and the following Dayhoff sequences: PRCRTI\_1, S75951, S74689, CELF37C4\_3, CRTI\_RHOCA, S76617, YNI2\_METTL, MTV014\_14, AOFB\_HUMAN, and MMU70429\_1.

**EXAMPLE 27: Isolation of cDNA clones Encoding Human PRO1063**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as ss.clu119743.init. The Incyte EST cluster sequence



ss.clu119743.init sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA48288.

In light of an observed sequence homology between the DNA48288 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2783726, the Incyte EST clone 2783726 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 65 and is herein designated DNA49820-1427.

The full length clone shown in Figure 65 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 90-92 and ending at the stop codon found at nucleotide positions 993-995 (Figure 65; SEQ ID NO:114). The predicted polypeptide precursor is 301 amino acids long, has a calculated molecular weight of approximately 33,530 daltons and an estimated pI of approximately 4.80. Analysis of the full-length PRO1063 sequence shown in Figure 66 (SEQ ID NO:115) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, potential N-glycosylation sites from about amino acid 195 to about amino acid 198, from about amino acid 217 to about amino acid 220 and from about amino acid 272 to about amino acid 275, a glycosaminoglycan attachment site from about amino acid 267 to about amino acid 270, a microbodies C-terminal targeting signal site from about amino acid 299 to about amino acid 301, a type II fibronectin collagen-binding domain homology sequence from about amino acid 127 to about amino acid 168 and a fructose-bisphosphate aldolase class II protein homology sequence from about amino acid 101 to about amino acid 118. Clone DNA49820-1427 has been deposited with the ATCC on June 2, 1998 and is assigned ATCC deposit no. 209932.

Analysis of the amino acid sequence of the full-length PRO1063 polypeptide suggests that it possesses sequence similarity to the human type IV collagenase protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1063 amino acid sequence and the following Dayhoff sequences, S68303, CFU68533\_1, P\_P91139, RNU65656\_1, PA2R\_RABIT, MMU56734\_1, FINC\_XENLA, A48925, P\_R92778 and FA12\_HUMAN.

#### EXAMPLE 28: Isolation of cDNA clones Encoding Human PRO619

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as 88434. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score



of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1656694, the Incyte EST clone 1656694 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 67 and is herein designated as DNA49821-1562.

The full length clone shown in Figure 67 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 81-83 and ending at the stop codon found at nucleotide positions 450-452 (Figure 67; SEQ ID NO:116). The predicted polypeptide precursor (Figure 68, SEQ ID NO:117) is 123 amino acids long including a predicted signal peptide at about amino acids 1-20. PRO619 has a calculated molecular weight of approximately 13,710 daltons and an estimated pI of approximately 5.19. Clone DNA49821-1562 was deposited with the ATCC on June 16, 1998 and is assigned ATCC deposit no. 209981.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 68 (SEQ ID NO:117), revealed significant homology between the PRO619 amino acid sequence and the following Dayhoff sequences: S35302, D87009\_1, HSU93494\_1, HUMIGLAM5\_1, D86999\_2, HUMIGLYM1\_1, HUMIGLYMKE\_1, A29491\_1, A29498\_1, and VPR2\_MOUSE.

#### EXAMPLE 29: Isolation of cDNA clones Encoding Human PRO943

A consensus DNA sequence encoding PRO943 was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence was then extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above. The extended consensus sequence is herein designated DNA36360. Based on the DNA36360 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO943.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CGAGATGACGCCGAGCCCCC-3' (SEQ ID NO:120)

reverse PCR primer 5'-CGGTTCGACACGCGGCAGGTG-3' (SEQ ID NO:121)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA36360 sequence which had the following nucleotide sequence

hybridization probe

5'-TGCTGCTCCTGCTGCCGCCGCTGCTGCTGGGGGCCTTCCCGCCGG-3' (SEQ ID NO:122)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO943 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO943 (designated herein as DNA52192-1369 [Figure 69, SEQ ID NO:118]) and the derived protein sequence for PRO943.

The entire nucleotide sequence of DNA52192-1369 is shown in Figure 69 (SEQ ID NO:118). Clone DNA52192-1369 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 150-152 and ending at the stop codon at nucleotide positions 1662-1664 (Figure 69). The predicted polypeptide precursor is 504 amino acids long (Figure 70). The full-length PRO943 protein shown in Figure 70 has an estimated molecular weight of about 54,537 daltons and a pI of about 10.04. Analysis of the full-length PRO943 sequence shown in Figure 70 (SEQ ID NO:119) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 17, a transmembrane domain from about amino acid 376 to about amino acid 396, tyrosine kinase phosphorylation sites from about amino acid 212 to about amino acid 219 and from about amino acid 329 to about amino acid 336, potential N-glycosylation sites from about amino acid 111 to about amino acid 114, from about amino acid 231 to about amino acid 234, from about amino acid 255 to about amino acid 258 and from about amino acid 293 to about amino acid 296 and an immunoglobulin and MHC protein sequence homology block from about amino acid 219 to about amino acid 236. Clone DNA52192-1369 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203042.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 70 (SEQ ID NO:119), evidenced significant homology between the PRO943 amino acid sequence and the following Dayhoff sequences: B49151, A39752, FGR1\_XENLA, S38579, RATHBFGFRB\_1, TVHU2F, FGR2\_MOUSE, CEK3\_CHICK, P\_R21080 and A27171\_1.

#### EXAMPLE 30: Isolation of cDNA clones Encoding Human PRO1188

A consensus DNA sequence was assembled relative to other EST sequences using the program "phrap" as described in Example 1 above. This consensus sequence is designated herein as DNA45679. Based on the DNA45679 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1188.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTGGTGCCTCAACAGGGAGCAG-3' (SEQ ID NO:125)

reverse PCR primer 5'-CCATTGTGCAGGTCAGGTCACAG-3' (SEQ ID NO:126)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45679 sequence which had the following nucleotide sequence:

hybridization probe

5'-CTGGAGCAAGTGCTCAGCTGCCTGTGGTCAGACTGGGGTC-3' (SEQ ID NO:127)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1188 gene using the probe oligonucleotide and one of the PCR primers. RNA

for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1188 (designated herein as DNA52598-1518 [Figure 71, SEQ ID NO:123]); and the derived protein sequence for PRO1188.

The entire coding sequence of PRO1188 is shown in Figure 71 (SEQ ID NO:123). Clone DNA52598-1518 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 136-138 and an apparent stop codon at nucleotide positions 3688-3690. The predicted polypeptide precursor is 1184 amino acids long. The full-length PRO1188 protein shown in Figure 72 has an estimated molecular weight of about 132,582 Daltons and a pI of about 8.80. Additional features include: a signal peptide at about amino acids 1-31; an ATP/GTP binding site motif A (P-loop) at about amino acids 266-273; an aldehyde dehydrogenases cysteine active site at about amino acids 188-199; growth factor and cytokines receptors family signature 2 at about amino acids 153-159; and potential N-glycosylation sites at about amino acids 129-132, 132-135, 346-349, 420-423, 550-553, 631-634, 1000-1003, and 1056-1059.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 72 (SEQ ID NO:124), revealed significant homology between the PRO1188 amino acid sequence and the following Dayhoff sequences: SSU83114\_1, S56015, CET21B6\_4, CELT19D2\_1, and TSP1\_MOUSE.

Clone DNA52598-1518 has been deposited with ATCC and is assigned ATCC deposit no 203107.

#### EXAMPLE 31: Isolation of cDNA clones Encoding Human PRO1133

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This sequence was extended using repeated cycles of phrap. The extended consensus sequence is designated herein DNA38102. Based on the DNA38102 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1133.

PCR primers (two forward and one reverse) were synthesized:

forward PCR primer 1 5'-TCGATTATGGACGAACATGGCAGC-3' (SEQ ID NO:130);

forward PCR primer 2 5'-TTCTGAGATCCCTCATCCTC-3' (SEQ ID NO:131); and

reverse primer 5'-AGGTTTCAGGGACAGCAAGTTTGGG-3' (SEQ ID NO:132).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA38102 sequence which had the following nucleotide sequence:

hybridization probe

5'TTTGCTGGACCTCGGCTACGGAATTGGCTTCCCTCTACGGACAGCTGGAT3' (SEQ ID NO:133).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with a PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1133 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1133 and the derived protein sequence for PRO1133.

The entire coding sequence of PRO1133 is shown in Figure 73 (SEQ ID NO:128). Clone DNA53913-1490 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 266-268 and an apparent stop codon at nucleotide positions 1580-1582 of SEQ ID NO:128. The predicted polypeptide precursor is 438 amino acids long. The signal peptide is at amino acids 1-18 of SEQ ID NO:129. EGF-like domain cysteine pattern signatures start at 315 and 385 of SEQ ID NO:129 as shown in Figure 74. Clone DNA53913-1490 has been deposited with ATCC and is assigned ATCC deposit no. 203162. The full-length PRO1133 protein shown in Figure 74 has an estimated molecular weight of about 49,260 daltons and a pI of about 6.15.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 74 (SEQ ID NO:129), revealed some sequence identity between the PRO1133 amino acid sequence and the following Dayhoff sequences (data from the database incorporated herein): AF002717\_1, LMG1\_HUMAN, B54665, UNC6\_CAEEL, LML1\_CAEEL, LMA5\_MOUSE, MMU88353\_1, LMA1\_HUMAN, HSLN2C64\_1 and AF005258\_1.

#### EXAMPLE 32: Isolation of cDNA clones Encoding Human PRO784

An initial DNA sequence (SEQ ID NO:136), referred to herein as DNA44661 and shown in Figure 77, was identified using a yeast screen, in a human fetal lung cDNA library that preferentially represents the 5' ends of the primary cDNA clones. DNA44661 was then compared to ESTs from public databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. The ESTs were then clustered and assembled into a consensus DNA sequence using the computer program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained is designated herein as "DNA45463". Based on the DNA45463 consensus sequence, oligonucleotides were synthesized for use as probes to isolate a clone of the full-length coding sequence for PRO784 from a human fetal lung cDNA library.

The full length DNA53978-1443 clone shown in Figure 75 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 37-39 and ending at the stop codon found at nucleotide positions 821-823 (Figure 75; SEQ ID NO:134). The predicted polypeptide precursor (Figure 76, SEQ ID NO:135) is 228 amino acids long. PRO784 has a calculated molecular weight of approximately 25,735 Daltons and an estimated pI of approximately 5.45. PRO784 has the following features: a signal peptide at about amino acid 1 to about 15; transmembrane domains at about amino acids 68 to about 87 and at about 183 to about 204; potential N-myristoylation sites at about amino acids 15-20, 51-56, 66-60, 163-168, and 206-211; and an RNP-1 protein RNA-binding region at about amino acids 108 to about 117.

Clone DNA53978-1443 was deposited with ATCC on June 16, 1998, and is assigned ATCC deposit no. 209983.

Based on a BLAST and FastA sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO784 shows amino acid sequence identity to the following proteins: RNU42209\_1,



MMU91538\_1, CGU91742\_1, CELF55A4\_6, SC22\_YEAST, and F48188.

**EXAMPLE 33: Isolation of cDNA Clones Encoding Human PRO783**

A yeast screening assay was employed to identify cDNA clones that encoded potential secreted proteins. Use of this yeast screening assay allowed identification of a single cDNA clone, designated herein as DNA45201 (Figure 80; SEQ ID NO:139).

The DNA45201 sequence was then used to search expressed sequence tag (EST) databases for the presence of potential homologies. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained is herein designated as "consen01". A proprietary Genentech EST sequence was used in the consensus assembly and is herein designated as DNA14575 (Figure 81; SEQ ID NO:140).

Based on the consen01 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO783. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GACTGTATCTGAGCCCCAGACTGC-3' (SEQ ID NO:141),

forward PCR primer 5'-TCAGCAATGAGGTGCTGCTC-3' (SEQ ID NO:142), and

reverse PCR primer 5'-TGAGGAAGATGAGGGACAGGTTGG-3' (SEQ ID NO:143).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consen01 sequence which had the following nucleotide sequence:

hybridization probe

5'-TATGGAAGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCC-3' (SEQ ID NO:144).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with a PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO783 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB228). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to Sall hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science,

253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO783 [herein designated as DNA53996-1442] (SEQ ID NO:137) and the derived protein sequence for PRO783.

5 The entire nucleotide sequence of DNA53996-1442 is shown in Figure 78 (SEQ ID NO:137). Clone DNA53996-1442 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 310-312 and ending at the stop codon at nucleotide positions 1777-1779 (Figure 78). The predicted polypeptide precursor is 489 amino acids long (Figure 79). The full-length PRO783 protein shown in Figure 79 has an estimated molecular weight of about 55,219 daltons and a pI of about 8.47. Analysis of the full-length PRO783 sequence shown in Figure 79 (SEQ ID NO:138) evidences the presence of the following features:

10 transmembrane domains located at about amino acids 23-42, 67-89, 111-135, 154-176, 194-218, 296-319, 348-370, 387-410 and 427-452; leucine zipper patterns located at about amino acids 263-283 and 399-420; a potential tyrosine kinase phosphorylation site at about amino acids 180-187; potential N-glycosylation sites at about amino acids 105 -108 and 121-124; potential cAMP- and a cGMP-dependent protein kinase phosphorylation site at about amino acids 288-291; and a region having sequence identity with bacterial

15 rhodopsins retinal binding site protein at about amino acids 190-218.

An analysis of the Dayhoff database (version 35.45 SwissProt 35) shows some sequence identity between the PRO783 amino acid sequence and the following Dayhoff sequences: YNC2\_CAEEL, D64048, ATAC002332\_3F4P9.3, NY2R\_SHEEP, and VSH\_MUMPA.

20 Clone DNA53996-1442 was deposited with the ATCC on June 2, 1998, and is assigned ATCC deposit no. 209921.

#### EXAMPLE 34: Isolation of cDNA Clones Encoding Human PRO820

25 An expressed sequence tag (EST) DNA database (Merck/Wash. U) was searched and an EST designated EST no. AA504080, Merck clone 825136, was identified (library 312, human B-cell tonsil). Homology searches revealed that this EST showed sequence identity with low affinity immunoglobulin gamma Fc receptor II. DNA sequencing gave the full-length DNA sequence for PRO820 and the derived protein sequence for PRO820.

30 The entire nucleotide sequence of DNA56041-1416 is shown in Figure 82 (SEQ ID NO:145). Clone DNA56041-1416 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 115-117 and ending at the stop codon at nucleotide positions 487-489 (Figure 82). The predicted polypeptide precursor is 124 amino acids long (Figure 83). The full-length PRO820 protein shown in Figure 83 has an estimated molecular weight of about 14,080 daltons and a pI of about 7.48. Clone DNA56041-1416 has been deposited with ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

35 Still analyzing the amino acid sequence of SEQ ID NO:146, the putative signal peptide is at about amino acids 1-15 of SEQ ID NO:146. Protein kinase C phosphorylation sites are at about amino acids 20-22 and 43-45 of SEQ ID NO:146. An N-myristoylation site is at about amino acids 89-94 of SEQ ID NO:146. An immunoglobulin and major histocompatibility complex domain is at about amino acids 83-90 of SEQ ID NO:146.

The corresponding nucleotides can be routinely determined given the sequences provided herein.

**EXAMPLE 35: Isolation of cDNA Clones Encoding Human PRO1080**

A consensus DNA sequence was assembled relative to other EST sequences using phrap and was extended using repeated cycles of BLAST and phrap so as to extend the consensus sequence as far as possible using the sources of the EST sequences as described in Example 1 above. The consensus sequence is designated herein as DNA52640. An EST proprietary to Genentech was employed in the consensus assembly and is herein designated as DNA36527 (Figure 86; SEQ ID NO:149).

In light of an observed sequence homology between the DNA36527 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 526423, the Merck EST clone 526423 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 84 and is herein designated as DNA56047-1456.

The entire nucleotide sequence of DNA56047-1456 is shown in Figure 84 (SEQ ID NO:147). Clone DNA56047-1456 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 159-161 and ending at the stop codon at nucleotide positions 1233-1235 of SEQ ID NO:147 (Figure 84). The predicted polypeptide precursor is 358 amino acids long (Figure 85). The full-length PRO1080 protein shown in Figure 85 has an estimated molecular weight of about 40,514 daltons and a pI of about 6.08. Clone DNA56047-1456 has been deposited with ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Also shown in Figure 85 are the approximate locations of the signal peptide, cell attachment site, Nt-DnaJ domain signature, region having sequence identity with Nt-DnaJ domain proteins, and N-glycosylation sites. The corresponding nucleic acids of these amino acid sequences and others provided herein can be routinely determined by the information provided herein.

**EXAMPLE 36: Isolation of cDNA Clones Encoding Human PRO1079**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above, and is herein designated DNA52714. Based on information provided by the assembly, the clone for Merck EST no. HO6898 was obtained and sequenced, thereby giving the nucleotide sequence designated herein as DNA56050-1455. The entire nucleotide sequence of DNA56050-1455 is shown in Figure 87 (SEQ ID NO:150). Clone DNA56050-1455 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 183-185 and ending at the stop codon at nucleotide positions 861-863 (Figure 87). The predicted polypeptide precursor is 226 amino acids long (Figure 88). The full-length PRO1079 protein shown in Figure 88 has an estimated molecular weight of about 24,611 Daltons and a pI of about 4.85. Analysis of the full-length PRO1079 sequence shown in Figure 88 (SEQ ID NO:3) evidences the presence of the following features: a signal peptide at about amino acid 1-29; potential N-myristoylation sites at about amino acids 10-15, and 51-56; homology to photosystem I psaG and psaK proteins at about amino acids 2 to 20; and homology to prolyl endopeptidase family serine proteins at about amino acids 150 to 163.

Analysis of the amino acid sequence of the full-length PRO1079 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO1079 amino acid sequence and the following Dayhoff sequences: CEK10C3\_4, MMU50734\_1, D69503, AF051149\_1, and VSMP\_CVMS.

Clone UNQ536 (DNA56050-1455) was deposited with the ATCC on June 22, 1998, and is assigned ATCC deposit no. 203011.

5

#### EXAMPLE 37: Isolation of cDNA clones Encoding Human PRO793

A cDNA clone (DNA56110-1437) encoding a native human PRO793 polypeptide was identified by a yeast screen, in a human skin tumor cDNA library that preferentially represents the 5' ends of the primary cDNA clones. The yeast screen employed identified a single EST clone designated herein as DNA50177 (Figure 91; SEQ ID NO:154). The DNA50177 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA50972.

In light of an observed sequence homology between the DNA50972 consensus sequence and an EST sequence encompassed within the Merck EST clone no. N33874, the Merck EST clone N33874 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 89 and is herein designated as DNA56110-1437.

The full-length DNA56110-1437 clone shown in Figure 89 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 77-79 and ending at the stop codon at nucleotide positions 491-493 (Figure 89). The predicted polypeptide precursor is 138 amino acids long (Figure 90). The full-length PRO793 protein shown in Figure 90 has an estimated molecular weight of about 15,426 daltons and a pI of about 10.67. Analysis of the full-length PRO793 sequence shown in Figure 90 (SEQ ID NO:153) evidences the presence of the following: transmembrane domains from about amino acid 12 to about amino acid 30, from about amino acid 33 to about amino acid 52, from about amino acid 69 to about amino acid 89 and from about amino acid 93 to about amino acid 109, potential N-myristoylation sites from about amino acid 11 to about amino acid 16, from about amino acid 51 to about amino acid 56 and from about amino acid 116 to about amino acid 121 and an amino acid sequence block having homology to an aminoacyl-transfer RNA synthetase class-II protein from about amino acid 49 to about amino acid 59. Clone DNA56110-1437 has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203113.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 90 (SEQ ID NO:153), evidenced certain homology between the PRO793 amino acid sequence and the following Dayhoff sequences: S47453, AF015193\_12, MTEHGNS9\_2, E64030, H69784, D64995, CD53\_MOUSE, GEN8006, AE001138\_7 and COX2\_STRPU.



**EXAMPLE 38: Isolation of cDNA Clones Encoding Human PRO1016**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. The consensus sequence obtained is herein designated DNA53502.

In light of an observed sequence homology between the DNA53502 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 38680, the Merck EST clone 38680 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 92.

The entire nucleotide sequence of DNA56113-1378 is shown in Figure 92 (SEQ ID NO:155). Clone DNA56113-1378 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 168-170 and ending at the stop codon at nucleotide positions 1302-1304 (Figure 92). The predicted polypeptide precursor is 378 amino acids long (Figure 93). The full-length PRO1016 protein shown in Figure 93 has an estimated molecular weight of about 44,021 daltons and a pI of about 9.07. Clone DNA56113-1378 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO1016 polypeptide suggests that portions of it possess sequence identity with acyltransferase, thereby indicating that PRO1016 may be a novel acyltransferase.

Still analyzing the amino acid sequence of SEQ ID NO:156, the putative signal peptide is at about amino acids 1-18 of SEQ ID NO:156. The transmembrane domain(s) are at about amino acids 332-352 and 305-330 of SEQ ID NO:156. The fructose-bisphosphate aldolase class-II protein homology sequence is at about amino acids 73-90 of SEQ ID NO:156. The extradiol ring-cleavage dioxygenase protein is at about amino acids 252-275 of SEQ ID NO:156. The corresponding nucleotides can be routinely determined given the sequences provided herein.

The specific Dayhoff database designation names of sequences to which PRO1016 has sequence identity with include the following: S52645, P\_R59712, P\_R99249, P\_R59713, BNAGPATRF\_1, CELT05H4\_15 and CELZK40\_1.

**EXAMPLE 39: Isolation of cDNA Encoding Human PRO1013**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. The consensus DNA sequence was then extended using repeated cycles of BLAST and phrap to extend the consensus sequence as far as possible using the sources of EST sequences.

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3107695, the Incyte EST clone 3107695 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 94 and is herein designated as DNA56410-1414.

The entire nucleotide sequence of DNA56410-1414 is shown in Figure 94 (SEQ ID NO:157). Clone DNA56410-1414 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 17-19 and ending at the stop codon at nucleotide positions 1244-1246 (Figure 94). The predicted

polypeptide precursor is 409 amino acids long (Figure 95). The full-length PRO1013 protein shown in Figure 95 has an estimated molecular weight of about 46,662 daltons and a pI of about 7.18. Clone DNA56410-1414 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

5 Still analyzing the amino acid sequence of SEQ ID NO:158, the putative signal peptide is at about amino acids 1-19 of SEQ ID NO:158. N-glycosylation sites are at about amino acids 75-78 and 322-325 of SEQ ID NO:158. An N-myristoylation site is at about amino acids 184-189 of SEQ ID NO:158. A growth factor and cytokine receptor family domain is at about amino acids 134-149 of SEQ ID NO:158. The corresponding nucleotides can be routinely determined given the sequences provided herein.

10 Blast analysis showed some sequence identity with other proteins. Specifically, PRO1013 has some sequence identity with at least the Dayhoff sequences designated: D63877\_1; MHU22019\_1, AE000730\_10, and AF019079\_1.

#### EXAMPLE 40: Isolation of cDNA Clones Encoding Human PRO937

15 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. That consensus sequence is herein designated DNA49651. Based on the DNA49651 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO937.

PCR primers (forward and reverse) were synthesized:

20 forward PCR primer 5'-CTCCGTGGTAAACCCACAGCCC-3' (SEQ ID NO:161); and  
reverse PCR primer 5'-TCACATCGATGGGATCCATGACCG-3' (SEQ ID NO:162).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA48651 sequence which had the following nucleotide sequence:

hybridization probe  
25 5'-GGTCTCGTGACTGTGAAGCCATGTTACAACACTGCTCAAACATCATGAG-3' (SEQ ID NO:163).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO937 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue (LIB227).

30 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO937 [herein designated as DNA56436-1448] (SEQ ID NO:159) and the derived protein sequence for PRO937.

35 The entire nucleotide sequence of DNA56436-1448 is shown in Figure 96 (SEQ ID NO:159). It contains a single open reading frame having an apparent translational initiation site at nucleotide positions 499-501 and ending at the stop codon found at nucleotide positions 2167-2169 (Figure 96, SEQ ID NO:159). The predicted polypeptide precursor is 556 amino acids long, has a calculated molecular weight of approximately 62,412 daltons and an estimated pI of approximately 6.62. Analysis of the full-length PRO937 sequence shown

in Figure 97 (SEQ ID NO:160) evidences the presence of the following features: signal peptide at about amino acids 1-22; ATP/GTP-binding site motif A (P-loop) at about amino acids 515-523; a potential N-glycosylation site at about amino acids 514-517; and sites of glypican homology at about amino acids 54-74, 106-156, 238-279, 309-345, 423-459, and 468-505.

5 Clone DNA56436-1448 has been deposited with ATCC on May 27, 1998, and is assigned ATCC deposit no. 209902.

Analysis of the amino acid sequence of the full-length PRO937 polypeptide suggests that it possesses significant sequence similarity to glypican proteins, thereby indicating that PRO937 may be a novel glypican protein. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO937 amino acid sequence and the following Dayhoff sequences:

10 GPCCK\_MOUSE, GPC2\_RAT, GPC5\_HUMAN, GPC3\_HUMAN, P\_R30168, CEC03H12\_2, GEN13820, HS119E23\_1, HDAC\_DROME, and AF017637\_1.

#### EXAMPLE 41: Isolation of cDNA clones Encoding Human PRO842

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single

15 Incyte EST cluster sequence designated herein as Incyte EST cluster sequence no. 69572. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a

20 BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA54230.

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA477092, the Merck EST clone AA477092 was purchased and

25 the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 98 and is herein designated as DNA56855-1447.

The full length clone shown in Figure 98 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 153-155 and ending at the stop codon found at nucleotide positions 510-512 (Figure 98; SEQ ID NO:164). The predicted polypeptide precursor (Figure 99, SEQ ID

30 NO:165) is 119 amino acids long. PRO842 has a calculated molecular weight of approximately 13,819 Daltons and an estimated pI of approximately 11.16. Other features of PRO842 include a signal peptide at about amino acids 1-22, a potential protein kinase C phosphorylation site at about amino acids 39-41 and two potential N-myristoylation sites at about amino acids 27-32 and about amino acids 46-51.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence

35 alignment analysis of the full-length sequence shown in Figure 98 (SEQ ID NO:164), evidenced some homology between the PRO842 amino acid sequence and the following Dayhoff sequences: CEZK131\_11, P\_R80843, RAT5HT2X\_1, S81882\_1, A60912, MCU60315\_137MC137L, U93422\_1, p\_P91996, U93462\_1, and

ZN18\_HUMAN.

Clone DNA56855-1447 was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no. 203004.

**EXAMPLE 42: Isolation of cDNA clones Encoding Human PRO839**

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte LIFESEQ® database, designated Incyte EST Cluster No. 24479. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using  
10 the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55709.

15 In light of an observed sequence homology between the DNA55709 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 754525, the Merck EST clone 754525 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 100 and is herein designated as DNA56859-1445.

20 The full length clone shown in Figure 100 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 2-4 and ending at the stop codon found at nucleotide positions 263-265 (Figure 100; SEQ ID NO:166). The predicted polypeptide precursor (Figure 101, SEQ ID NO:167) is 87 amino acids long. PRO839 has a calculated molecular weight of approximately 9,719 Daltons and an estimated pI of approximately 4.67. Other features of PRO839 include a signal peptide at about amino acids 1-23, potential protein kinase C phosphorylation sites at about amino acids 37-39 and about amino acids 85-87,  
25 a potential casein kinase II phosphorylation site at about amino acids 37-40, sequence identity with ribonucleotide reductase large subunit protein at about amino acids 50-60, and sequence identity with eukaryotic RNA-binding region RNP-1 proteins at about amino acids 70-79.

30 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 101 (SEQ ID NO:167), evidenced some homology between the PRO839 amino acid sequence and the following Dayhoff sequences: CD14\_MOUSE, XPR6\_YARLI, HS714385\_1, S49783, BB19\_RABIT, GVPH-HALME, AB003135\_1, P\_R85453, LUU27081\_2, and TP2B\_MOUSE.

Clone DNA56859-1445 was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no.209019.



**EXAMPLE 43: Isolation of cDNA Clones Encoding Human PRO1180**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence (Incyte EST cluster sequence no. 14732). The Incyte EST cluster sequence no. 14732 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55711.

In light of an observed sequence homology between the DNA55711 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T60981, the Merck EST clone T60981 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 102 and is herein designated DNA56860-1510.

The full length clone shown in Figure 102 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 78-80 and ending at the stop codon found at nucleotide positions 909-911 (Figure 102; SEQ ID NO:168). The predicted polypeptide precursor is 277 amino acids long, has a calculated molecular weight of approximately 31,416 daltons and an estimated pI of approximately 8.88. Analysis of the full-length PRO1180 sequence shown in Figure 103 (SEQ ID NO:169) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, a leucine zipper pattern sequence from about amino acid 10 to about amino acid 31, and potential N-myristylation sites from about amino acid 64 to about amino acid 69, from about amino acid 78 to about amino acid 83, from about amino acid 80 to about amino acid 85, from about amino acid 91 to about amino acid 96 and from about amino acid 201 to about amino acid 206. Clone DNA56860-1510 has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209952.

Analysis of the amino acid sequence of the full-length PRO1180 polypeptide suggests that it possesses sequence similarity to the methyltransferase family of proteins. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1180 amino acid sequence and the following Dayhoff sequences, MTCI65\_14, D69267, YH09\_YEAST, BIOC\_SERMA, ATAC00448415T1D16.16, SHGCPIR\_18, SPBC3B9\_4, AB009504\_14, P\_W17977 and A69952.

**EXAMPLE 44: Isolation of cDNA clones Encoding Human PRO1134**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 7511. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or

in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55725. Two proprietary Genentech EST sequences were employed in the assembly and are shown in Figure 106 (SEQ ID NO:172) and Figure 107 (SEQ ID NO:173).

5 In light of an observed sequence homology between the DNA55725 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H94897, the Merck EST clone H94897 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 106 and is herein designated as DNA56865-1491.

10 Clone DNA56865-1491 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 153-155 and ending at the stop codon at nucleotide positions 1266-1268 (Figure 104). The predicted polypeptide precursor is 371 amino acids long (Figure 105). The full-length PRO1134 protein shown in Figure 105 has an estimated molecular weight of about 41,935 daltons and a pI of about 9.58. Analysis of the full-length PRO1134 sequence shown in Figure 105 (SEQ ID NO:171) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, potential N-glycosylation sites from  
15 about amino acid 103 to about amino acid 106, from about amino acid 249 to about amino acid 252 and from about amino acid 257 to about amino acid 260, and an amino acid block having homology to tyrosinase CuA-binding region proteins from about amino acid 280 to about amino acid 306. Clone DNA56865-1491 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203022.

20 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 105 (SEQ ID NO:171), evidenced significant homology between the PRO1134 amino acid sequence and the following Dayhoff sequences: F20P5\_18, AC002396\_10, S47847, C64146, GSPA\_BACSU, P\_W10564, RFAI\_ECOLI, Y258\_HAEIN, RFAJ\_SALTY and P\_R32985.

#### 25 EXAMPLE 45: Isolation of cDNA clones Encoding Human PRO830

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incytedatabase, designated 20251. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing  
30 homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55733.

35 In light of an observed sequence homology between the DNA55733 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H78534, the Merck EST clone H78534 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 108 and is herein designated as DNA56866-1342.

Clone DNA56866-1342 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 154-156 and ending at the stop codon at nucleotide positions 415-417 (Figure 108). The predicted polypeptide precursor is 87 amino acids long (Figure 109). The full-length PRO830 protein shown in Figure 109 has an estimated molecular weight of about 9,272 daltons and a pI of about 9.19. Analysis of the full-length PRO830 sequence shown in Figure 109 (SEQ ID NO:175) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 33, potential N-myristoylation sites from about amino acid 2 to about amino acid 7 and from about amino acid 8 to about amino acid 13 and a thioredoxin family of proteins homology block from about amino acid 23 to about amino acid 39. Clone UNQ470 (DNA56866-1342) has been deposited with ATCC on June 22, 1998 and is assigned ATCC deposit no. 203023.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 109 (SEQ ID NO:175), evidenced significant homology between the PRO830 amino acid sequence and the following Dayhoff sequences: HSU88154\_1, HSU88153\_1, SAPKSGENE\_1, HPU31791\_5, GGCNOT2\_1, CPU91421\_1, CHKESTPC09\_1, PQ0769, U97553\_79 and B60095.

#### EXAMPLE 46: Isolation of cDNA clones Encoding Human PRO1115

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, designated Incyte EST cluster sequence no. 165008. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55726.

In light of an observed sequence homology between the DNA55726 consensus sequence and an EST sequence encompassed within the Merck EST clone no. R75784, the Merck EST clone R75784 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 111 and is herein designated as DNA56868-1478.

The full length clone shown in Figure 110 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 189-191 and ending at the stop codon found at nucleotide positions 1524-1526 (Figure 110; SEQ ID NO:176). The predicted polypeptide precursor (Figure 111, SEQ ID NO:177) is 445 amino acids long. PRO1115 has a calculated molecular weight of approximately 50,533 Daltons and an estimated pI of approximately 8.26. Additional features include a signal peptide at about amino acids 1-20; potential N-glycosylation sites at about amino acids 204-207, 295-298, and 313-316; and putative transmembrane domains at about amino acids 35-54, 75-97, 126-146, 185-204, 333-350, and 353-371.



An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 111 (SEQ ID NO:177), evidenced some amino acid sequence identity between the PRO1115 amino acid sequence and the following Dayhoff sequences: AF053947\_79, S73698, CEC47A10\_4, CCOMTND5G\_1, HS4LMP2AC\_1, LMP2\_EBV, PA24\_MOUSE, HCU33331\_7, P-W05508, and AF002273\_1.

5        Clone DNA56868-1478 was deposited with the ATCC on June 23, 1998 and is assigned ATCC deposit no. 203024..

**EXAMPLE 47: Isolation of cDNA clones Encoding Human PRO1277**

10        A consensus DNA sequence was assembled relative to other ESTs using repeated cycles of BLAST and the program "phrap" as described in Example 1 above. One or more of the ESTs from the assembly was derived from diseased coronary artery tissue. The consensus sequence obtained is designated herein as "DNA49434".

15        In light of an observed sequence homology between the DNA49434 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3042605, the Incyte EST clone 3042605 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 112 (SEQ ID NO:178).

20        Clone DNA56869-1545 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 188-190, and an apparent stop codon at nucleotide positions 2222-2224 (Figure 112). The predicted polypeptide precursor is 678 amino acids long (Figure 113). The full-length PRO1277 protein shown in Figure 113 has an estimated molecular weight of about 73,930 daltons and a pI of about 9.48. Additional features include a signal peptide at about amino acids 1-26; a transmembrane domain at about amino acids 181-200, and potential N-glycosylation sites at about amino acids 390-393 and 520-523.

25        An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 113 (SEQ ID NO:179), revealed significant homology between the PRO1277 amino acid sequence and Dayhoff sequence no AF012252\_1. Homology was also found between the PRO1277 amino acid sequence and the following Dayhoff sequences: AF006740\_1, CA36\_HUMAN, HSU1\_1, HUMCOL7A1X\_1, CA17\_HUMAN, MMZ78163\_1, CAMA\_CHICK, HSU69263\_1, YNX3\_CAEEL, and MMRNAM3\_1.

30        Clone DNA56869-1545 has been deposited with ATCC and is assigned ATCC deposit no. 203161.

**EXAMPLE 48: Isolation of cDNA Clones Encoding Human PRO1135**

35        A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA52767. Based on the DNA52767 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1135.



In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with PCR primer pairs prepared based upon the DNA52767 sequence. A positive library was then used to isolate clones encoding the PRO1135 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human coronary artery smooth muscle tissue (LIB309). The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to Sall hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1135 [herein designated as DNA56870-1492] (SEQ ID NO:180) and the derived protein sequence for PRO1135.

The entire nucleotide sequence of DNA56870-1492 is shown in Figure 114 (SEQ ID NO:180). Clone DNA56870-1492 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 62-64 and ending at the stop codon at nucleotide positions 1685-1687 (Figure 114). The predicted polypeptide precursor is 541 amino acids long (Figure 115). The full-length PRO1135 protein shown in Figure 115 has an estimated molecular weight of about 60,335 daltons and a pI of about 5.26. Analysis of the full-length PRO1135 sequence shown in Figure 115 (SEQ ID NO:181) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 21, potential N-glycosylation sites from about amino acid 53 to about amino acid 56, from about amino acid 75 to about amino acid 78, from about amino acid 252 to about amino acid 255 and from about amino acid 413 to about amino acid 416 and an amino acid block having homology to glycosyl hydrolase family 35 proteins from about amino acid 399 to about amino acid 414. Clone DNA56870-1492 has been deposited with ATCC on June 2, 1998 and is assigned ATCC deposit no. 209925.

Analysis of the amino acid sequence of the full-length PRO1135 polypeptide suggests that it possesses significant sequence similarity to the alpha 1,2-mannosidase protein, thereby indicating that PRO1135 may be a novel mannosidase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO1135 amino acid sequence and the following Dayhoff sequences, DMC86E4\_5, D86967\_1, SPAC23A1\_4, YH04\_YEAST, B54408, SS MAN9MAN\_1, CEZC410\_4, S61631 and MSU14190\_1.

#### EXAMPLE 49: Isolation of cDNA Clones Encoding Human PRO1114

A cDNA sequence isolated in the amylase screen described in Example 2 above was found, by the WU-BLAST-2 sequence alignment computer program, to have certain sequence identity to other known interferon receptors. This cDNA sequence is herein designated DNA48466 and is shown in Figure 118 (SEQ ID NO:184).

Based on the sequence identity, probes were generated from the sequence of the DNA48466 molecule and used to screen a human breast carcinoma library (LIB135) prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes

et al., Science, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

The oligonucleotide probes employed were as follows:

forward PCR primer 5'-AGGCTTCGCTGCGACTAGACCTC-3' (SEQ ID NO:185)

reverse PCR primer 5'-CCAGGTCGGGTAAGGATGGTTGAG-3' (SEQ ID NO:186)

hybridization probe

5 5'-TTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGC-3' (SEQ ID NO:187)

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 250-252, and a stop signal at nucleotide positions 1183-1185 (Figure 116, SEQ ID NO:182). The predicted polypeptide precursor is 311 amino acids long, has a calculated molecular weight of approximately 35,076 daltons and an estimated pI of approximately 5.04. Analysis of the full-length PRO1114 interferon receptor sequence shown in Figure 117 (SEQ ID NO:183) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 29, a transmembrane domain from about amino acid 230 to about amino acid 255, potential N-glycosylation sites from about amino acid 40 to about amino acid 43 and from about amino acid 134 to about amino acid 137, an amino acid sequence block having homology to tissue factor proteins from about amino acid 92 to about amino acid 119 and an amino acid sequence block having homology to integrin alpha chain proteins from about amino acid 232 to about amino acid 262. Clone DNA57033-1403 has been deposited with ATCC on May 27, 1998 and is assigned ATCC deposit no. 209905.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 117 (SEQ ID NO:183), evidenced significant homology between the PRO1114 interferon receptor amino acid sequence and the following Dayhoff sequences: G01418, INR1\_MOUSE, P\_R71035, INGS\_HUMAN, A26595\_1, A26593\_1, I56215 and TF\_HUMAN.

#### EXAMPLE 50: Isolation of cDNA Clones Encoding Human PRO828

A consensus DNA sequence was identified using the method described in Example 1 above. This consensus sequence is herein designated DNA35717. Based on the DNA35717 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO828.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCAGGACTTCTACGACTTCAAGGC-3' (SEQ ID NO:190); and

reverse PCR primer 5'-AGTCTGGGCCAGGTACTTGAAGGC-3' (SEQ ID NO:191).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35717 sequence which had the following nucleotide sequence:

hybridization probe

5'-CAACATCCGGGGCAAACCTGGTGTCTGCTGGAGAAGTACCGCGGATCGGTGT-3' (SEQ ID NO:192)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO828 gene using the probe oligonucleotide and one of the PCR primers. RNA

for construction of the cDNA libraries was isolated from human fetal lung tissue (LIB25).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO828 [herein designated as DNA57037-1444] (SEQ ID NO:188) and the derived protein sequence for PRO828.

5 The entire nucleotide sequence of DNA57037-1444 is shown in Figure 119 (SEQ ID NO:188). Clone DNA57037-1444 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 34-36 and ending at the stop codon at nucleotide positions 595-597 (Figure 119). The predicted polypeptide precursor is 187 amino acids long (Figure 120). The full-length PRO828 protein shown in Figure 120 has an estimated molecular weight of about 20,996 daltons and a pI of about 8.62. Analysis of the full-length PRO828 sequence shown in Figure 120 (SEQ ID NO:189) evidences the presence of the following: a  
10 signal peptide at about amino acids 1- 21; sequences identity to glutathione peroxidases signature 2 at about amino acids 82-89; sequence identity to glutathione peroxidases selenocysteine proteins at about amino acids 35-60, 63-100, 107-134, and 138-159. Clone DNA57037-1444 has been deposited with ATCC on May 27, 1998, and is assigned ATCC deposit no. 209903.

Analysis of the amino acid sequence of the full-length PRO828 polypeptide suggests that it possesses  
15 significant sequence similarity to glutathione peroxidases, thereby indicating that PRO828 may be a novel peroxidase enzyme. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO828 amino acid sequence and the following Dayhoff sequences: AF053311\_1, CELT09A12\_2, AC004151\_3, BTUE\_ECOLI, CER05H10\_3, P\_P80918, PWU88907\_1, and P\_W22308.

20

EXAMPLE 51: Isolation of cDNA clones Encoding Human PRO1009

A cDNA clone (DNA57129-1413) encoding a native human PRO1009 polypeptide was identified by the use of a yeast screen, in a human SK-Lu-1 adenocarcinoma cell line cDNA library that preferentially represents the 5' ends of the primary cDNA clones. First SEQ ID NO:195 (Figure 123) was identified, which  
25 was extended by alignments to other EST sequences to form a consensus sequence. Oligonucleotide probes based upon the consensus sequence were synthesized and used to screen the cDNA library which gave rise to the full-length DNA57129-1413 clone.

The full length DNA57129-1413 clone shown in Figure 121 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 41-43 and ending at the stop codon found at  
30 nucleotide positions 1886-1888 (Figure 121; SEQ ID NO:193). The predicted polypeptide precursor (Figure 122, SEQ ID NO:194) is 615 amino acids long. Figure 122 also shows the approximate locations of the signal sequence, transmembrane domains, myristoylation sites, a glycosylation site and an AMP-binding domain. PRO1009 has a calculated molecular weight of approximately 68,125 daltons and an estimated pI of approximately 7.82. Clone DNA57129-1413 has been deposited with ATCC and is assigned ATCC deposit no.  
35 209977. It is understood that the deposited clone has the actual and correct sequence and that the representations herein may have minor, normal sequencing errors.

Based on a WU-BLAST-2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1009 shows amino acid sequence identity to at least the following proteins which were designated in a Dayhoff database as follows: F69893, CEF28F8\_2, BSY13917\_7, BSY13917\_7, D69187, D69649, XCRPFB\_1, E64928, YDID\_ECOLI, BNACSF8\_1 and RPU75363\_2.

5 **EXAMPLE 52: Isolation of cDNA Clones Encoding Human PRO1007**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated as DNA40671.

10 In light of an observed sequence homology between the DNA40671 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T70513, the Merck EST clone T70513 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 124.

15 The entire nucleotide sequence of DNA57690-1374 is shown in Figure 124 (SEQ ID NO:196). Clone DNA57690-1374 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 16-18 and ending at the stop codon at nucleotide positions 1054-1056 (Figure 124). The predicted polypeptide precursor is 346 amino acids long (Figure 125). The full-length PRO1007 protein shown in Figure 125 has an estimated molecular weight of about 35,971 daltons and a pI of about 8.17. Clone DNA57690-1374 has been deposited with the ATCC on June 9, 1998. Regarding the sequence, it is understood that the deposited clone contains the actual sequence, and the sequences provided herein are based on known sequencing techniques. The representative figures herein show the representative numbering.

20 Analysis of the amino acid sequence of the full-length PRO1007 polypeptide suggests that portions of it possess sequence identity to MAGPIAP, thereby indicating that PRO1007 may be a novel member of the family to which MAGPIAP belongs.

25 Still analyzing the amino acid sequence of SEQ ID NO:197, the putative signal peptide is at about amino acids 1-30 of SEQ ID NO:197. The transmembrane domain is at amino acids 325-346 of SEQ ID NO:197. N-glycosylation sites are at about amino acids 118-121, 129-132, 163-166, 176-179, 183-186 and 227-230 of SEQ ID NO:197. Ly-6/u-Par domain protein homology is at about amino acids 17-36 and 209-222 of SEQ ID NO:197. The corresponding nucleotides of the amino acids presented herein can be routinely determined given the sequences provided herein.

30 **EXAMPLE 53: Isolation of cDNA clones Encoding Human PRO1056**

35 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated herein as 6425. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a



consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55736.

In light of an observed sequence homology between the DNA55736 consensus sequence and an EST sequence encompassed within the Merck EST clone no. R88049, the Merck EST clone R88049 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

5 The sequence of this cDNA insert is shown in Figure 126 and is herein designated as DNA57693-1424.

Clone DNA57693-1424 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 56-58 and ending at the stop codon at nucleotide positions 416-418 (Figure 126). The predicted polypeptide precursor is 120 amino acids long (Figure 127). The full-length PRO1056 protein shown in Figure 127 has an estimated molecular weight of about 13,345 daltons and a pI of about 5.18. Analysis of  
10 the full-length PRO1056 sequence shown in Figure 127 (SEQ ID NO:199) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 18, a transmembrane domain from about amino acid 39 to about amino acid 58, a potential N-glycosylation site from about amino acid 86 to about amino acid 89, protein kinase C phosphorylation sites from about amino acid 36 to about amino acid 38 and from about amino acid 58 to about amino acid 60, a tyrosine kinase phosphorylation site from about amino acid 25 to about  
15 amino acid 32 and an amino acid sequence block having homology to channel forming colicin proteins from about amino acid 24 to about amino acid 56. Clone DNA57693-1424 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203008.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 127 (SEQ ID NO:199), evidenced significant  
20 homology between the PRO1056 amino acid sequence and the following Dayhoff sequences: PLM\_HUMAN, A40533, ATNG\_HUMAN, A55571, ATNG\_SHEEP, S31524, GEN13025, RIC\_MOUSE, A48678 and A10871\_1.

#### EXAMPLE 54: Isolation of cDNA clones Encoding Human PRO826

25 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 47283. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul  
30 et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56000.

In light of an observed sequence homology between the DNA56000 consensus sequence and an EST  
35 sequence encompassed within the Merck EST clone no. W69233, the Merck EST clone W69233 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 128 and is herein designated as DNA57694-1341.

Clone DNA57694-1341 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 13-15 and ending at the stop codon at nucleotide positions 310-312 (Figure 128). The predicted polypeptide precursor is 99 amino acids long (Figure 129). The full-length PRO826 protein shown in Figure 129 has an estimated molecular weight of about 11,050 daltons and a pI of about 7.47. Analysis of the full-length PRO826 sequence shown in Figure 129 (SEQ ID NO:201) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 22, potential N-myristoylation sites from about amino acid 22 to about amino acid 27 and from about amino acid 90 to about amino acid 95 and an amino acid sequence block having homology to peroxidase from about amino acid 16 to about amino acid 48. Clone DNA57694-1341 has been deposited with ATCC on June 22, 1998 and is assigned ATCC deposit no. 203017.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 129 (SEQ ID NO:201), evidenced significant homology between the PRO826 amino acid sequence and the following Dayhoff sequences: CCU12315\_1, SCU96108\_6, CELF39F10\_4 and HELT\_HELHO.

**EXAMPLE 55: Isolation of cDNA clones Encoding Human PRO819**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 49605. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56015.

In light of an observed sequence homology between the DNA56015 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H65785, the Merck EST clone H65785 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 130 and is herein designated as DNA57695-1340.

Clone DNA57695-1340 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 46-48 and ending at the stop codon at nucleotide positions 202-204 (Figure 130). The predicted polypeptide precursor is 52 amino acids long (Figure 131). The full-length PRO819 protein shown in Figure 131 has an estimated molecular weight of about 5,216 daltons and a pI of about 4.67. Analysis of the full-length PRO819 sequence shown in Figure 131 (SEQ ID NO:203) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a potential N-myristoylation site from about amino acid 2 to about amino acid 7 and a region having homology to immunoglobulin light chain from about amino acid 5 to about amino acid 33. Clone DNA57695-1340 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203006.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 131 (SEQ ID NO:203), evidenced significant homology between the PRO819 amino acid sequence and the following Dayhoff sequences: HSU03899\_1, HUMIGLITEB\_1, VG28\_HSVSA, AF031522\_1, PAD1\_YEAST and AF045484\_1.

#### 5 EXAMPLE 56: Isolation of cDNA Clones Encoding Human PRO1006

An initial candidate sequence from Incyte cluster sequence no. 45748 was identified using the signal algorithm process described in Example 3 above. This sequence was then aligned with a variety of public and Incyte EST sequences and a consensus sequence designated herein as DNA56036 was derived therefrom.

10 In light of an observed sequence homology between the DNA56036 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 489737, the Merck EST clone 489737 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 132.

The entire nucleotide sequence of DNA57699-1412 is shown in Figure 132 (SEQ ID NO:204). Clone DNA57699-1412 contains a single open reading frame with an apparent translational initiation site at nucleotide  
15 positions 28-30 and ending at the stop codon at nucleotide positions 1204-1206 (Figure 132). The predicted polypeptide precursor is 392 amino acids long (Figure 133). The full-length PRO1006 protein shown in Figure 133 has an estimated molecular weight of about 46,189 daltons and a pI of about 9.04. Clone DNA57699-1412 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

20 Analyzing the amino acid sequence of SEQ ID NO:205, the putative signal peptide is at about amino acids 1-23 of SEQ ID NO:205. The N-glycosylation sites are at about amino acids 40-43, 53-56, 204-207 and 373-376 of SEQ ID NO:205. An N-myristoylation site is at about amino acids 273-278 of SEQ ID NO:205.

The corresponding nucleotides of these amino acid regions and others can be routinely determined given the sequences provided herein.

25

#### EXAMPLE 57: Isolation of cDNA Clones Encoding Human PRO1112

Use of the signal sequence algorithm described in Example 3 above allowed identification of a specific EST cluster sequence. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database  
30 (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is  
35 herein designated DNA56018.

In light of an observed sequence homology between the DNA56018 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA223546, the Merck EST clone AA223546 was



purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 134 and is herein designated as DNA57702-1476.

The entire nucleotide sequence of DNA57702-1476 is shown in Figure 134 (SEQ ID NO:206). Clone DNA57702-1476 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 20-22 and ending at the stop codon at nucleotide positions 806-808 of SEQ ID NO:206 (Figure 134).

5 The predicted polypeptide precursor is 262 amino acids long (Figure 135). The full-length PRO1112 protein shown in Figure 135 has an estimated molecular weight of about 29,379 daltons and a pI of about 8.93. Figure 135 also shows the approximate locations of the signal peptide and transmembrane domains. Clone DNA57702-1476 has been deposited with the ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

10 Analysis of the amino acid sequence of the full-length PRO1112 polypeptide suggests that it possesses some sequence similarity to other proteins. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO1112 amino acid sequence and at least the following Dayhoff sequences, MTY20B11\_13 (a mycobacterium tuberculosis peptide), F64471, AE000690\_6, XLU16364\_1, E43259 (H<sup>+</sup>-transporting ATP synthase) and PIGSLADRXE\_1 (MHC class II  
15 histocompatibility antigen).

#### EXAMPLE 58: Isolation of cDNA clones Encoding Human PRO1074

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence (Incyte cluster sequence No. 42586). This cluster sequence was then compared to  
20 a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ<sup>TM</sup>, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus  
25 DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56251.

In light of an observed sequence homology between the DNA56251 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA081912, the Merck EST clone AA081912 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length  
30 protein. The sequence of this cDNA insert is shown in Figure 136 and is the full-length DNA sequence for PRO1074. Clone DNA57704-1452 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209953.

The entire nucleotide sequence of DNA57704-1452 is shown in Figure 136 (SEQ ID NO:208). Clone DNA57704-1452 contains a single open reading frame with an apparent translational initiation site at nucleotide  
35 positions 322-324 and ending at the stop codon at nucleotide positions 1315-1317 (Figure 136). The predicted polypeptide precursor is 331 amino acids long (Figure 137). The full-length PRO1074 protein shown in Figure 137 has an estimated molecular weight of about 39,512 Daltons and a pI of about 8.03. Analysis of the full-



length PRO1074 sequence shown in Figure 137 (SEQ ID NO:209) evidences the presence of the following features: a transmembrane domain at about amino acids 20 to 39; potential N-glycosylation sites at about amino acids 72 to 75, 154 to 157, 198 to 201, 212 to 215, and 326 to 329; a glycosaminoglycan attachment site at about amino acids 239 to 242, and a Ly-6/u-PAR domain at about amino acids 23 to 36.

5 Analysis of the amino acid sequence of the full-length PRO1074 polypeptide suggests that it possesses significant sequence similarity to beta 1,3-galactosyltransferase, thereby indicating that PRO1074 may be a novel member of the galactosyltransferase family of proteins. Analysis of the amino acid sequence of the full-length PRO1074 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1074 amino acid sequence and the following Dayhoff sequences: AF029792\_1, P\_R57433, DMU41449\_1, AC000348\_14, P\_R47479, CET09F5\_2, CEF14B6\_4, CET15D6\_5, CEC54C8\_4, and  
10 CEE03H4\_10.

Clone DNA57704-1452 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209953.

EXAMPLE 59: Isolation of cDNA clones Encoding Human PRO1005

15 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, Incyte cluster sequence no. 49243. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or  
20 BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56380.

In light of an observed sequence homology between the DNA56380 consensus sequence and an EST  
25 sequence encompassed within the Merck EST clone no. AA256657, the Merck EST clone AA256657 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 138 and is herein designated as DNA57708-1411.

The full length clone shown in Figure 138 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 30-32 and ending at the stop codon found at nucleotide positions  
30 585-587 (Figure 138; SEQ ID NO:210). The predicted polypeptide precursor (Figure 139, SEQ ID NO:211) is 185 amino acids long. PRO1005 has a calculated molecular weight of approximately 20,331 daltons and an estimated pI of approximately 5.85. Clone DNA57708-1411 was deposited with the ATCC June 23, 1998, and is assigned ATCC deposit no. 203021.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence  
35 alignment analysis of the full-length sequence shown in Figure 139 (SEQ ID NO:211), evidenced some homology between the PRO1005 amino acid sequence and the following Dayhoff sequences: DDU07187\_1, DDU87912\_1, CELD1007\_14, A42239, DDU42597\_1, CYAG\_DICDI, S50452, MRKC\_KLEPN, P-R41998,

and XYNA\_RUMFL.

**EXAMPLE 60: Isolation of cDNA clones Encoding Human PRO1073**

An initial DNA sequence referred to herein as DNA55938 and shown in Figure 142 (SEQ ID NO:214) was identified using a yeast screen, in a human SK-Lu-1 adenocarcinoma cell line cDNA library that preferentially represents the 5' ends of the primary cDNA clones. DNA55938 was then compared to ESTs from public databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., *Methods in Enzymology*, 266:460-480 (1996)]. The ESTs were clustered and assembled into a consensus DNA sequence using the computer program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained is designated herein as DNA56411.

In light of an observed sequence homology between the DNA56411 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H86027, the Merck EST clone H86027 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 140.

The full length DNA57710-1451 clone shown in Figure 140 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 345-347 and ending at the stop codon found at nucleotide positions 1242-1244 (Figure 140; SEQ ID NO:212). The predicted polypeptide precursor (Figure 141, SEQ ID NO:213) is 299 amino acids long. PRO1073 has a calculated molecular weight of approximately 34,689 daltons and an estimated pI of approximately 11.49. The PRO1073 polypeptide has the following additional features: a signal peptide at about amino acids 1-31, sequence identity to bZIP transcription factor basic domain signature at about amino acids, a potential N-glycosylation site at about amino acids 2-5, and sequence identity with protamine P1 proteins at about amino acids 158-183.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 141 (SEQ ID NO:213), revealed some sequence identity between the PRO1073 amino acid sequence and the following Dayhoff sequences: MMU37351\_1, ATAC00250510T9J22.10, S59043, ENXNUPR\_1, B47328, SR55\_DROME, S26650, SON\_HUMAN, VIT2\_CHICK, and XLC4SRPRT\_1.

Clone DNA57710-1451 was deposited with the ATCC on July 1, 1998 and is assigned ATCC deposit no. 203048.

**EXAMPLE 61: Isolation of cDNA clones Encoding Human PRO1152**

A cDNA clone (DNA57711-1501) encoding a native human PRO1152 polypeptide was identified by employing a yeast screen, in a human infant brain cDNA library that preferentially represents the 5' ends of the primary cDNA clones. Specifically, a yeast screen was employed to identify a cDNA designated herein as DNA55807 (SEQ ID NO:217; see Figure 145).

In light of an observed sequence homology between the DNA55807 sequence and an EST sequence encompassed within the Merck EST clone no. R56756, the Merck EST clone R56756 was purchased and the

cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 143.

The full-length DNA57711-1501 clone shown in Figure 143 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon at nucleotide positions 1495-1497 (Figure 143). The predicted polypeptide precursor is 479 amino acids long (Figure 144).

5 The full-length PRO1152 protein shown in Figure 144 has an estimated molecular weight of about 53,602 daltons and a pI of about 8.82. Analysis of the full-length PRO1152 sequence shown in Figure 144 (SEQ ID NO:216) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, transmembrane domains from about amino acid 133 to about amino acid 155, from about amino acid 168 to about amino acid 187, from about amino acid 229 to about amino acid 247, from about amino acid 264 to about amino acid 285, from about amino acid 309 to about amino acid 330, from about amino acid 371 to about amino acid 390 and from about amino acid 441 to about amino acid 464, potential N-glycosylation sites from about amino acid 34 to about amino acid 37 and from about amino acid 387 to about amino acid 390 and an amino acid sequence block having homology to a respiratory-chain NADH dehydrogenase subunit from about amino acid 243 to about amino acid 287. Clone DNA57711-1501 has been deposited with ATCC on July 1, 1998 and is  
10 assigned ATCC deposit no. 203047.  
15

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST-2 sequence alignment analysis of the full-length sequence shown in Figure 144 (SEQ ID NO:216), evidenced significant homology between the PRO1152 amino acid sequence and the following Dayhoff sequences: AF052239\_1, SYNN9CGA\_1, SFCYTB2\_1, GEN12507, P\_R11769, MTV025\_109, C61168, S43171, P\_P61689 and  
20 P\_P61696.

#### EXAMPLE 62: Isolation of cDNA clones Encoding Human PRO1136

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 109142. This EST cluster sequence was then compared  
25 to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus  
30 DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56039.

In light of an observed sequence homology between the DNA56039 consensus sequence and an EST sequence encompassed within the Merck EST clone no. HSC1NF011, the Merck EST clone HSC1NF011 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length  
35 protein. The sequence of this cDNA insert is shown in Figure 146 and is herein designated as DNA57827-1493.

Clone DNA57827-1493) contains a single open reading frame with an apparent translational initiation site at nucleotide positions 216-218 and ending at the stop codon at nucleotide positions 2112-2114 (Figure 146).

The predicted polypeptide precursor is 632 amino acids long (Figure 147). The full-length PRO1136 protein shown in Figure 147 has an estimated molecular weight of about 69,643 daltons and a pI of about 8.5. Analysis of the full-length PRO1136 sequence shown in Figure 147 (SEQ ID NO:219) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 15 and potential N-glycosylation sites from about amino acid 108 to about amino acid 111, from about amino acid 157 to about amino acid 160, from about amino acid 289 to about amino acid 292 and from about amino acid 384 to about amino acid 387. Clone DNA57827-1493 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203045.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 147 (SEQ ID NO:219), evidenced significant homology between the PRO1136 amino acid sequence and the following Dayhoff sequences: AF034746\_1, AF034745\_1, MMAF000168\_19, HSMUPP1\_1, AF060539\_1, SP97\_RAT, I38757, MMU93309\_1, CEK01A6\_4 and HSA224747\_1.

#### EXAMPLE 63: Isolation of cDNA clones Encoding Human PRO813

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence (Incyte EST cluster sequence no. 45501. The Incyte EST cluster sequence no. 45501 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56400.

In light of an observed sequence homology between the DNA56400 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T90592, the Merck EST clone T90592 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 148 and is herein designated DNA57834-1339.

The full length clone shown in Figure 148 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 109-111 and ending at the stop codon found at nucleotide positions 637-639 (Figure 149; SEQ ID NO:221). The predicted polypeptide precursor is 176 amino acids long, has a calculated molecular weight of approximately 19,616 daltons and an estimated pI of approximately 7.11. Analysis of the full-length PRO813 sequence shown in Figure 149 (SEQ ID NO:221) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 26 and potential N-myristoylation sites from about amino acid 48 to about amino acid 53, from about amino acid 153 to about amino acid 158, from about amino acid 156 to about amino acid 161 and from about amino acid 167 to about amino acid 172. Clone DNA57834-1339 has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209954.



Analysis of the amino acid sequence of the full-length PRO813 polypeptide suggests that it possesses sequence similarity to the pulmonary surfactant-associated protein C. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO813 amino acid sequence and the following Dayhoff sequences, PSPC\_MUSVI, P\_P92071, G02964, P\_R65489, P\_P82977, P\_R84555, S55542, MUSIGHAJ\_1 and PH1158.

**EXAMPLE 64: Isolation of cDNA Clones Encoding Human PRO809**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence. The Incyte EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., *Methods in Enzymology* 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56418.

In light of an observed sequence homology between the DNA56418 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H74302, the Merck EST clone H74302 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 150 and is herein designated DNA57836-1338.

The entire nucleotide sequence of DNA57836-1338 is shown in Figure 150 (SEQ ID NO:222). Clone DNA57836-1338 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 63-65 and ending at the stop codon at nucleotide positions 858-860 of SEQ ID NO:222 (Figure 150). The predicted polypeptide precursor is 265 amino acids long (Figure 151). The full-length PRO809 protein shown in Figure 151 has an estimated molecular weight of about 29,061 daltons and a pI of about 9.18. Figure 151 further shows the approximate positions of the signal peptide and N-glycosylation sites. The corresponding nucleotides can be determined by referencing Figure 150. Clone DNA57836-1338 has been deposited with ATCC on June 23, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO809 polypeptide suggests that it possesses some sequence similarity to the heparin sulfate proteoglycan and to endothelial cell adhesion molecule-1. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO809 amino acid sequence and the following Dayhoff sequences, PGBM\_MOUSE, D82082\_1 and PW14158.

**EXAMPLE 65: Isolation of cDNA Clones Encoding Human PRO791**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence. The Incyte EST cluster sequence was then compared to a variety of expressed

sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56429.

In light of an observed sequence homology between the DNA56429 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 36367, the Merck EST clone 36367 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 152 and is herein designated DNA57838-1337.

The entire nucleotide sequence of DNA57838-1337 is shown in Figure 152 (SEQ ID NO:224). Clone DNA57838-1337 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 9-11 and ending at the stop codon at nucleotide positions 747-749 of SEQ ID NO:224 (Figure 152). The predicted polypeptide precursor is 246 amino acids long (Figure 153). The full-length PRO791 protein shown in Figure 153 has an estimated molecular weight of about 27,368 daltons and a pI of about 7.45. Figure 153 also shows the approximate locations of the signal peptide, the transmembrane domain, N-glycosylation sites and a region conserved in extracellular proteins. The corresponding nucleotides of one embodiment provided herein can be identified by referencing Figure 152. Clone DNA57838-1337 has been deposited with ATCC on June 23, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO791 polypeptide suggests that it has sequence similarity with MHC-I antigens, thereby indicating that PRO791 may be related to MHC-I antigens. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some sequence identity between the PRO791 amino acid sequence and the following Dayhoff sequences, AF034346\_1, MMQ1K5\_1 and HFE\_HUMAN.

#### EXAMPLE 66: Isolation of cDNA clones Encoding Human PRO1004

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence, Incyte cluster sequence No. 73681. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated as DNA56516.

In light of an observed sequence homology between the DNA56516 consensus sequence and an EST sequence encompassed within the Merck EST clone no. H43837, the Merck EST clone H43837 was purchased

and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 154.

The full length clone shown in Figure 154 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 119-121 and ending at the stop codon at nucleotide positions 464-466 (Figure 154; SEQ ID NO:226). The predicted polypeptide precursor is 115 amino acids long (Figure 155; SEQ ID NO:227). The full-length PRO1004 protein shown in Figure 155 has an estimated molecular weight of about 13,649 daltons and a pI of about 9.58. Analysis of the full-length PRO1004 sequence shown in Figure 155 (SEQ ID NO:227) evidences the presence of the following features: a signal peptide at about amino acids 1-24, a microbodies C-terminal targeting signal at about amino acids 113-115, a potential N-glycosylation site at about amino acids 71-74, and a domain having sequence identity with dihydrofolate reductase proteins at about amino acids 22-48.

Analysis of the amino acid sequence of the full-length PRO1004 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1004 amino acid sequence and the following Dayhoff sequences: CELR02D3\_7, LECI\_MOUSE, AF006691\_3, SSZ97390\_1, SSZ97395\_1, and SSZ97400\_1.

Clone DNA57844-1410 was deposited with the ATCC on June 23, 1998, and is assigned ATCC deposit no. 203010.

#### EXAMPLE 67: Isolation of cDNA clones Encoding Human PRO1111

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which had homology to insulin-like growth factor binding protein.

RNA for construction of cDNA libraries was isolated from human fetal brain. The cDNA libraries used to isolate the cDNA clones encoding human PRO1111 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., *Science*, 253:1278-1280 (1991)) in the unique XhoI and NotI.

The human fetal brain cDNA libraries (prepared as described above), were screened by hybridization with a synthetic oligonucleotide probe based upon the Incyte EST sequence described above:

5'-CCACCACCTGGAGGTCCTGCAGTTGGGCAGGAAGTCCATCCGGCAGATTG-3' (SEQ ID NO:251).

An identified cDNA clone was sequenced in entirety. The entire nucleotide sequence of PRO1111 is shown in Figure 156 (SEQ ID NO:228). Clone DNA58721-1475 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 57-59 and a stop codon at nucleotide positions 2016-2018 (Figure 156; SEQ ID NO:228). The predicted polypeptide precursor is 653 amino acids long (Figure 157). The transmembrane domains are at positions 21-40 (type II) and 528-548. Clone DNA58721-1475 has been deposited with ATCC and is assigned ATCC deposit no. 203110. The full-length PRO1111 protein shown in Figure 157 has an estimated molecular weight of about 72,717 daltons and a pI of about 6.99.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 157 (SEQ ID NO:229), revealed some sequence identity between the PRO1111 amino acid sequence and the following Dayhoff sequences: A58532, D86983\_1, RNPLGPV\_1, PGS2\_HUMAN, AF038127\_1, ALS\_MOUSE, GPV\_HUMAN, PGS2\_BOVIN, ALS\_PAPPA and I47020.

5

**EXAMPLE 68: Isolation of cDNA clones Encoding Human PRO1344**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA33790. Based on the DNA33790 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1344.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-AGGTTCTGTGATGGAGACAACCGCG-3' (SEQ ID NO:232)

reverse PCR primer 5'-TGTC AAGGACGCACTGCCGTCATG-3' (SEQ ID NO:233)

15 Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA33790 sequence which had the following nucleotide sequence

hybridization probe

5'-TGGCCAGATCATCAAGCGTGTCTGTGGCAACGAGCGGCCAGCTCCTATCC-3' (SEQ ID NO:234)

20 In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1344 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney tissue.

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1344 (designated herein as DNA58723-1588 [Figure 158, SEQ ID NO:230]); and the derived protein sequence for PRO1344.

30 The entire nucleotide sequence of DNA58723-1588 is shown in Figure 158 (SEQ ID NO:230). Clone DNA58723-1588 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 26-28 and ending at the stop codon at nucleotide positions 2186-2188 (Figure 158). The predicted polypeptide precursor is 720 amino acids long (Figure 159). The full-length PRO1344 protein shown in Figure 159 has an estimated molecular weight of about 80,199 daltons and a pI of about 7.77. Analysis of the full-length PRO1344 sequence shown in Figure 159 (SEQ ID NO:231) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, an EGF-like domain cysteine protein signature sequence from about amino acid 260 to about amino acid 271, potential N-glycosylation sites from about amino acid 96 to about amino acid 99, from about amino acid 279 to about amino acid 282, from about amino acid 316 to about amino acid 319, from about amino acid 451 to about amino acid 454 and from about amino acid 614 to about amino acid 617, an amino acid sequence block having homology to serine proteases, trypsin family from about amino acid 489 to about amino acid 505 and a CUB domain protein profile sequence from about amino



acid 150 to about amino acid 166. Clone DNA58723-1588 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203133.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 159 (SEQ ID NO:231), evidenced significant homology between the PRO1344 amino acid sequence and the following Dayhoff sequences: S77063\_1, CRAR\_MOUSE, P\_R74775, P\_P90070, P\_R09217, P\_P70475, HSBMP16\_1 and U50330\_1.

**EXAMPLE 69: Isolation of cDNA clones Encoding Human PRO1109**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA52642. The consensus DNA sequence was obtained by extending using repeated cycles of BLAST and phrap a previously obtained consensus sequence as far as possible using the sources of EST sequences discussed above. Based on the DNA52642 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1109.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCTTACCTCAGAGGCCAGAGCAAGC-3' (SEQ ID NO:237)

reverse PCR primer 5'-GAGCTTCATCCGTTCTGCGTTCACC-3' (SEQ ID NO:238)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA52642 sequence which had the following nucleotide sequence

hybridization probe

5'-CAGGAATGTAAAGCTTTACAGAGGGTCGCCATCCTCGTTCCCCACC-3' (SEQ ID NO:239)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1109 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human SK-Lu-1 adenocarcinoma cell tissue (LIB247).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1109 (designated herein as DNA58737-1473 [Figure 160, SEQ ID NO:235]) and the derived protein sequence for PRO1109.

The entire nucleotide sequence of DNA58737-1473 is shown in Figure 160 (SEQ ID NO:235). Clone DNA58737-1473 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 119-120 and ending at the stop codon at nucleotide positions 1151-1153 (Figure 160). The predicted polypeptide precursor is 344 amino acids long (Figure 161). The full-length PRO1109 protein shown in Figure 161 has an estimated molecular weight of about 40,041 daltons and a pI of about 9.34. Analysis of the full-length PRO1109 sequence shown in Figure 161 (SEQ ID NO:236) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 27, potential N-glycosylation sites from about amino acid 4 to about amino acid 7, from about amino acid 220 to about amino acid 223 and from about amino acid 335 to about amino acid 338 and an amino acid sequence block having homology to xylose isomerase proteins from about amino acid 191 to about amino acid 201. Clone DNA58737-1473 has been deposited with ATCC

on August 18, 1998 and is assigned ATCC deposit no. 203136.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 161 (SEQ ID NO:236), evidenced significant homology between the PRO1109 amino acid sequence and the following Dayhoff sequences: HSUDPGAL\_1, HSUDPB14\_1, NALS\_BOVIN, HSU10473\_1, CEW02B12\_11, YNJ4\_CAEEL, AE000738\_11, CET24D1\_1, S48121 and CEGLY9\_1.

#### EXAMPLE 70: Isolation of cDNA clones Encoding Human PRO1383

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA53961. Based on the DNA53961 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1383.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CATTTCTTACCCTGGACCCAGCTCC-3' (SEQ ID NO:242)

reverse PCR primer 5'-GAAAGGCCACAGCACATCTGGCAG-3' (SEQ ID NO:243)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA53961 sequence which had the following nucleotide sequence

hybridization probe

5'-CCACGACCCGAGCAACTTCCTCAAGACCGACTTGTTTCTCTACAGC-3' (SEQ ID NO:244)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1383 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal brain tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1383 (designated herein as DNA58743-1609 [Figure 162, SEQ ID NO: 240]) and the derived protein sequence for PRO1383.

The entire nucleotide sequence of DNA58743-1609 is shown in Figure 162 (SEQ ID NO:240). Clone DNA58743-1609 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 122-124 and ending at the stop codon at nucleotide positions 1391-1393 (Figure 162). The predicted polypeptide precursor is 423 amino acids long (Figure 163). The full-length PRO1383 protein shown in Figure 163 has an estimated molecular weight of about 46,989 daltons and a pI of about 6.77. Analysis of the full-length PRO1383 sequence shown in Figure 163 (SEQ ID NO:241) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a transmembrane domain from about amino acid 339 to about amino acid 362, and potential N-glycosylation sites from about amino acid 34 to about amino acid 37, from about amino acid 58 to about amino acid 61, from about amino acid 142 to about amino acid 145, from about amino acid 197 to about amino acid 200, from about amino acid 300 to about amino acid 303 and from about amino acid 364 to about amino acid 367. Clone DNA58743-1609 has been deposited with ATCC on

August 25, 1998 and is assigned ATCC deposit no. 203154.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 163 (SEQ ID NO:241), evidenced significant homology between the PRO1383 amino acid sequence and the following Dayhoff sequences: NMB\_HUMAN, QNR\_COTJA, P\_W38335, P115\_CHICK, P\_W38164, A45993\_1, MMU70209\_1, D83704\_1 and P\_W39176.

#### EXAMPLE 71: Isolation of cDNA Clones Encoding Human PRO1003

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as 43055. This sequence was then compared to a variety of EST databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated consen01.

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2849382, the Incyte EST clone 2849382 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 164.

The entire nucleotide sequence of DNA58846-1409 is shown in Figure 164 (SEQ ID NO:245). Clone DNA58846-1409 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 41-43 and ending at the stop codon at nucleotide positions 293-295 (Figure 164). The predicted polypeptide precursor is 84 amino acids long (Figure 165). The full-length PRO1003 protein shown in Figure 165 has an estimated molecular weight of about 9,408 daltons and a pI of about 9.28. Analysis of the full-length PRO1003 sequence shown in Figure 165 (SEQ ID NO:246) evidences the presence of a signal peptide at amino acids 1 to about 24, and a cAMP- and cGMP-dependent protein kinase phosphorylation site at about amino acids 58 to about 61. Analysis of the amino acid sequence of the full-length PRO1003 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1003 amino acid sequence and the following Dayhoff sequences: AOPCZA363\_3, SRTX\_ATREN, A48298, MHVJHMS\_1, VGL2\_CVMJH, DHDHTC2\_2, CORT\_RAT, TAL6\_HUMAN, P\_W14123, and DVUFI\_2.

#### EXAMPLE 72: Isolation of cDNA Clones Encoding Human PRO1108

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA53237.

In light of an observed sequence homology between the DNA53237 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2379881, the Incyte EST clone 2379881 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 166 and is herein designated DNA58848-1472.

The entire nucleotide sequence of DNA58848-1472 is shown in Figure 166 (SEQ ID NO:247). Clone DNA58848-1472 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 77-79 and ending at the stop codon at nucleotide positions 1445-1447 (Figure 166). The predicted polypeptide precursor is 456 amino acids long (Figure 167). The full-length PRO1108 protein shown in Figure 167 has an estimated molecular weight of about 52,071 daltons and a pI of about 9.46. Analysis of the full-length PRO1108 sequence shown in Figure 167 (SEQ ID NO:248) evidences the presence of the following: type II transmembrane domains from about amino acid 22 to about amino acid 42, from about amino acid 156 to about amino acid 176, from about amino acid 180 to about amino acid 199 and from about amino acid 369 to about amino acid 388, potential N-glycosylation sites from about amino acid 247 to about amino acid 250, from about amino acid 327 to about amino acid 330, from about amino acid 328 to about amino acid 331 and from about amino acid 362 to about amino acid 365 and an amino acid block having homology to ER lumen protein retaining receptor protein from about amino acid 153 to about amino acid 190. Clone DNA58848-1472 has been deposited with ATCC on June 9, 1998 and is assigned ATCC deposit no. 209955.

Analysis of the amino acid sequence of the full-length PRO1108 polypeptide suggests that it possesses significant sequence similarity to the LPAAT protein, thereby indicating that PRO1108 may be a novel LPAAT homolog. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO1108 amino acid sequence and the following Dayhoff sequences, AF015811\_1, CER07E3\_2, YL35\_CAEEL, S73863, CEF59F4\_4, P\_W06422, MMU41736\_1, MTV008\_39, P\_R99248 and Y67\_BPT7.

#### EXAMPLE 73: Isolation of cDNA Clones Encoding Human PRO1137

The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Using this procedure, Incyte EST No. 3459449, also referred to herein as "DNA7108", was identified as an EST having a BLAST score of 70 or greater that did not encode a known protein.

A consensus DNA sequence was assembled relative to the DNA7108 sequence and other ESTs using repeated cycles of BLAST and the program "phrap" (Phil Green, Univ. of Washington, Seattle, WA). The consensus sequence obtained therefrom is referred to herein as DNA53952.

In light of an observed sequence homology between the DNA53952 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3663102, the Incyte EST clone 3663102 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 168.



The entire nucleotide sequence of DNA58849-1494 is shown in Figure 168 (SEQ ID NO:249). Clone DNA58849-1494 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 77-79 and ending at the stop codon at nucleotide positions 797-799 (Figure 168). The predicted polypeptide precursor is 240 amino acids long (Figure 169). The full-length PRO1137 protein shown in Figure 169 has an estimated molecular weight of about 26,064 daltons and a pI of about 8.65. Analysis of the full-length PRO1137 sequence shown in Figure 169 (SEQ ID NO:250) evidences the presence of a signal peptide at about amino acids 1 to 14 and a potential N-glycosylation site at about amino acids 101-105.

Analysis of the amino acid sequence of the full-length PRO1137 polypeptide suggests that it possesses significant sequence similarity to ribosyltransferase thereby indicating that PRO1137 may be a novel member of the ribosyltransferase family of proteins. Analysis of the amino acid sequence of the full-length PRO1137 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1137 amino acid sequence and the following Dayhoff sequences: MMART5\_1, NARG\_MOUSE, GEN11909, GEN13794, GEN14406, MMRNART62\_1, and P\_R41876.

#### EXAMPLE 74: Isolation of cDNA clones Encoding Human PRO1138

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence, Incyte cluster sequence no. 165212. This cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated as DNA54224. The assembly included a proprietary Genentech EST designated herein as DNA49140 (Figure 172; SEQ ID NO:254).

In light of an observed sequence homology between the DNA54224 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3836613, the Incyte EST clone 3836613 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 170 and is the full-length DNA sequence for PRO1138. Clone DNA58850-1495 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209956.

The entire nucleotide sequence of DNA58850-1495 is shown in Figure 170 (SEQ ID NO:252). Clone DNA58850-1495 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 38-40 and ending at the stop codon at nucleotide positions 1043-1045 (Figure 170). The predicted polypeptide precursor is 335 amino acids long (Figure 171). The full-length PRO1138 protein shown in Figure 171 has an estimated molecular weight of about 37,421 Daltons and a pI of about 6.36. Analysis of the full-length PRO1138 sequence shown in Figure 171 (SEQ ID NO:253) evidences the presence of the following features: a signal peptide at about amino acid 1 to about amino acid 22; a transmembrane domain at about amino

acids 224 to about 250; a leucine zipper pattern at about amino acids 229 to about 250; and potential N-glycosylation sites at about amino acids 98-101, 142-145, 148-151, 172-175, 176-179, 204-207, and 291-295.

Analysis of the amino acid sequence of the full-length PRO1138 polypeptide suggests that it possesses significant sequence similarity to the CD84, thereby indicating that PRO1138 may be a novel member of the Ig superfamily of polypeptides. More particularly, analysis of the amino acid sequence of the full-length PRO1138 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1138 amino acid sequence and the following Dayhoff sequences: HSU82988\_1, HUMLY9\_1, P\_R97631, P\_R97628, P\_R97629, P\_R97630, CD48\_RAT, CD2\_HUMAN, P\_P93996, and HUMBGP\_1.

Clone DNA58850-1495 was deposited with ATCC on June 9, 1998, and is assigned ATCC deposit no. 209956.

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EXAMPLE 75: Isolation of cDNA clones Encoding Human PRO1054

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 66212. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55722.

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In light of an observed sequence homology between the DNA55722 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 319751, the Incyte EST clone 319751 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 173 and is herein designated as DNA58853-1423.

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Clone DNA58853-1423 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 46-48 and ending at the stop codon at nucleotide positions 586-588 (Figure 173). The predicted polypeptide precursor is 180 amino acids long (Figure 174). The full-length PRO1054 protein shown in Figure 174 has an estimated molecular weight of about 20,638 daltons and a pI of about 5.0. Analysis of the full-length PRO1054 sequence shown in Figure 174 (SEQ ID NO:256) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 18, a leucine zipper pattern from about amino acid 155 to about amino acid 176 and amino acid sequence blocks having homology to lipocalin proteins from about amino acid 27 to about amino acid 38 and from about amino acid 110 to about amino acid 120. Clone DNA58853-1423 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203016.

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An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 174 (SEQ ID NO:256), evidenced significant homology between the PRO1054 amino acid sequence and the following Dayhoff sequences: MUP1\_MOUSE, MUP6\_MOUSE, MUP2\_MOUSE, MUP8\_MOUSE, MUP5\_MOUSE, MUP4\_MOUSE, S10124,

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MUPM\_MOUSE, MUP\_RAT and ECU70823\_1.

**EXAMPLE 76: Isolation of cDNA clones Encoding Human PRO994**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 157555. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55728.

In light of an observed sequence homology between the DNA55728 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2860366, the Incyte EST clone 2860366 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 175 and is herein designated as DNA58855-1422.

Clone DNA58855-1422 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 31-33 and ending at the stop codon at nucleotide positions 718-720 (Figure 175). The predicted polypeptide precursor is 229 amino acids long (Figure 176). The full-length PRO994 protein shown in Figure 176 has an estimated molecular weight of about 25,109 daltons and a pI of about 6.83. Analysis of the full-length PRO994 sequence shown in Figure 176 (SEQ ID NO:258) evidences the presence of the following: transmembrane domains from about amino acid 10 to about amino acid 31, from about amino acid 50 to about amino acid 72, from about amino acid 87 to about amino acid 110 and from about amino acid 191 to about amino acid 213, potential N-glycosylation sites from about amino acid 80 to about amino acid 83, from about amino acid 132 to about amino acid 135, from about amino acid 148 to about amino acid 151 and from about amino acid 163 to about amino acid 166 and an amino acid block having homology to TNFR/NGFR cysteine-rich region proteins from about amino acid 4 to about amino acid 11. Clone DNA58855-1422 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203018.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 176 (SEQ ID NO:258), evidenced significant homology between the PRO994 amino acid sequence and the following Dayhoff sequences: AF027204\_1, TAL6\_HUMAN, ILT4\_HUMAN, JC6205, MMU57570\_1, S40363, ETU56093\_1, S42858, P\_R66849 and P\_R74751.

**EXAMPLE 77: Isolation of cDNA clones Encoding Human PRO812**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 170079. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank)



and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The  
5 consensus sequence obtained therefrom is herein designated as DNA55721.

In light of an observed sequence homology between the DNA55721 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 388964, the Incyte EST clone 388964 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 177 and is herein designated as DNA59205-1421.

10 Clone DNA59205-1421 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 55-57 and ending at the stop codon at nucleotide positions 304-306 (Figure 177). The predicted polypeptide precursor is 83 amino acids long (Figure 178). The full-length PRO812 protein shown in Figure 178 has an estimated molecular weight of about 9,201 daltons and a pI of about 9.3. Analysis of the full-length PRO812 sequence shown in Figure 178 (SEQ ID NO:260) evidences the presence of the following:  
15 a signal peptide from about amino acid 1 to about amino acid 15, a cAMP- and cGMP-dependent protein kinase phosphorylation site from about amino acid 73 to about amino acid 76 and protein kinase C phosphorylation sites from about amino acid 70 to about amino acid 72 and from about amino acid 76 to about amino acid 78. Clone DNA59205-1421 has been deposited with ATCC on June 23, 1998 and is assigned ATCC deposit no. 203009.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence  
20 alignment analysis of the full-length sequence shown in Figure 178 (SEQ ID NO:260), evidenced significant homology between the PRO812 amino acid sequence and the following Dayhoff sequences: P\_W35802, P\_W35803, PSC1\_RAT, S68231, GEN13917, PSC2\_RAT, CC10\_HUMAN, UTER\_RABIT, AF008595\_1 and A56413.

#### 25 EXAMPLE 78: Isolation of cDNA clones Encoding Human PRO1069

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence designated herein as 100727. This sequence was then compared to a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in  
30 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56001.

In light of an observed sequence homology between the DNA56001 consensus sequence and an EST  
35 sequence encompassed within the Incyte EST clone no. 3533881, the Incyte EST clone 3533881 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 179 and is the full-length DNA sequence for PRO1069.



Clone DNA59211-1450 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209960.

The entire nucleotide sequence of DNA59211-1450 is shown in Figure 179 (SEQ ID NO:261). Clone DNA59211-1450 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 197-199 and ending at the stop codon at nucleotide positions 464-466. The predicted polypeptide precursor is 89 amino acids long (Figure 180). The full-length PRO1069 protein shown in Figure 180 has an estimated molecular weight of about 9,433 daltons and a pI of about 8.21. Analysis of the full-length PRO1069 sequence shown in Figure 180 (SEQ ID NO:262) evidences the presence of the following features: a signal peptide sequence at amino acid 1 to about 16; a transmembrane domain at about amino acids 36 to about 59; potential N-myristoylation sites at about amino acids 41-46, 45-50, and 84-89; and homology with extracellular proteins SCP/Tpx-1/Ag5/PR-1/Sc7 at about amino acids 54 to about 66.

Analysis of the amino acid sequence of the full-length PRO1069 polypeptide suggests that it possesses significant sequence similarity to CHIF, thereby indicating that PRO1069 may be a member of the CHIF family of polypeptides. More particularly, analysis of the amino acid sequence of the full-length PRO1069 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1069 amino acid sequence and the following Dayhoff sequences: CHIF\_RAT, A55571, PLM\_HUMAN, A40533, ATNG\_BOVIN, RIC\_MOUSE, PETD\_SYNY3, VTBI\_XENLA, A05009, and S75086.

Clone DNA59211-1450 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209960.

## 20 EXAMPLE 79: Isolation of cDNA Clones Encoding Human PRO1129

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as 98833. The Incyte EST cluster sequence no. 98833 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56038.

30 In light of an observed sequence homology between the DNA56038 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1335241, the Incyte EST clone 1335241 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 181 and is herein designated DNA59213-1487.

35 The full length clone shown in Figure 181 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 42-44 and ending at the stop codon found at nucleotide positions 1614-1616 (Figure 181; SEQ ID NO:263). The predicted polypeptide precursor is 524 amino acids long, has a calculated molecular weight of approximately 60,310 daltons and an estimated pI of approximately 7.46.

Analysis of the full-length PRO1129 sequence shown in Figure 182 (SEQ ID NO:264) evidences the presence of the following: type II transmembrane domains from about amino acid 13 to about amino acid 32 and from about amino acid 77 to about amino acid 102, a cytochrome P-450 cysteine heme-iron ligand signature sequence from about amino acid 461 to about amino acid 470 and potential N-glycosylation sites from about amino acid 112 to about amino acid 115 and from about amino acid 168 to about amino acid 171. Clone DNA59213-1487 has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209959.

Analysis of the amino acid sequence of the full-length PRO1129 polypeptide suggests that it possesses sequence similarity to the cytochrome P-450 family of proteins. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1129 amino acid sequence and the following Dayhoff sequences, AC004523\_1, S45702, AF054821\_1 and I53015.

#### EXAMPLE 80: Isolation of cDNA clones Encoding Human PRO1068

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the LIFESEQ® database, designated Incyte cluster no. 141736. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. One or more of the ESTs was derived from a human mast cell line from a patient with mast cell leukemia. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56094.

In light of an observed sequence homology between the DNA56094 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 004974, the Incyte EST clone 004974 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 183 and is herein designated as DNA59214-1449 (SEQ ID NO:265).

The full length clone shown in Figure 183 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 42-44 and ending at the stop codon found at nucleotide positions 414-416 (Figure 183; SEQ ID NO:265). The predicted polypeptide precursor (Figure 184, SEQ ID NO:266) is 124 amino acids long. PRO1068 has a calculated molecular weight of approximately 14,284 daltons and an estimated pI of approximately 8.14. The PRO1068 polypeptide has the following additional features, as indicated in Figure 184: a signal peptide sequence at about amino acids 1-20, a urotensin II signature sequence at about amino acids 118-123, a cell attachment sequence at about amino acids 64-66, and a potential cAMP- and cGMP-dependent protein kinase phosphorylation site at about amino acids 112-115.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 184 (SEQ ID NO:266), revealed homology between the PRO1068 amino acid sequence and the following Dayhoff sequences: HALBOP\_1, MTV043\_36,

I50498, and P\_R78445

Clone DNA59214-1449 was deposited with the ATCC on July 1, 1998 and is assigned ATCC deposit no.203046.

**EXAMPLE 81: Isolation of cDNA clones Encoding Human PRO1066**

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST cluster sequence designated herein as 79066. The Incyte EST cluster sequence no. 79066 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or  
10 BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56121.

In light of an observed sequence homology between the DNA56121 consensus sequence and an EST  
15 sequence encompassed within the Incyte EST clone no. 1515315, the Incyte EST clone 1515315 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 185 and is herein designated DNA59215-1425.

The full length clone shown in Figure 185 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 176-178 and ending at the stop codon found at nucleotide  
20 positions 527-529 (Figure 185; SEQ ID NO:267). The predicted polypeptide precursor is 117 amino acids long, has a calculated molecular weight of approximately 12,911 daltons and an estimated pI of approximately 5.46. Analysis of the full-length PRO1066 sequence shown in Figure 186 (SEQ ID NO:268) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 23, a cAMP- and cGMP-dependent protein kinase phosphorylation site from about amino acid 38 to about amino acid 41 and potential  
25 N-myristoylation sites from about amino acid 5 to about amino acid 10, from about amino acid 63 to about amino acid 68 and from about amino acid 83 to about amino acid 88. Clone UNQ524 (DNA59215-1425) has been deposited with the ATCC on June 9, 1998 and is assigned ATCC deposit no. 209961.

Analysis of the amino acid sequence of the full-length PRO1066 polypeptide suggests that it does not possess significant sequence similarity to any known human protein. However, an analysis of the Dayhoff  
30 database (version 35.45 SwissProt 35) evidenced some degree of homology between the PRO1066 amino acid sequence and the following Dayhoff sequences, MOTI\_HUMAN, AF025667\_1, MTCY19H9\_8 and RABIGKCH\_1.

**EXAMPLE 82: Isolation of cDNA Clones Encoding Human PRO1184**

35 Use of the signal sequence algorithm described in Example 3 on ESTs from an Incyte database allowed identification a candidate sequence designated herein as DNA56375. This sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and



a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56375.

In light of an observed sequence homology between the DNA56375 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1428374, the Incyte EST clone 1428374 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 187.

The full length clone shown in Figure 187 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 106-108 and ending at the stop codon found at nucleotide positions 532-534 (Figure 187; SEQ ID NO:269). The predicted polypeptide precursor is 142 amino acids long, has a calculated molecular weight of approximately 15,690 daltons and an estimated pI of approximately 9.64. Analysis of the full-length PRO1184 sequence shown in Figure 188 (SEQ ID NO:270) evidences the presence of a signal peptide at about amino acids 1-38. Clone DNA59220-1514 has been deposited with the ATCC on June 9, 1998. It is understood that the deposited clone has the actual sequences and that representations are presented herein.

Analysis of the amino acid sequence of the full-length PRO1184 polypeptide suggests that it possesses some sequence identity with a protein called TIM from *Drosophila virilis*, designated "DVTIMS02\_1" in the Dayhoff data base, (version 35.45 SwissProt 35). Other Dayhoff database (version 35.45 SwissProt 35) sequences having some degree of sequence identity with PRO1184 include: WIS1\_SCHPO, F002186\_1, ATAC00239124 and MSAIPRP\_1.

#### EXAMPLE 83: Isolation of cDNA clones Encoding Human PRO1360

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST sequence from an Incyte database, designated DNA10572. This EST sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank, Merck/Wash. U.) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57314.

In light of an observed sequence homology between the DNA57314 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA406443, the Merck EST clone AA406443 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 189 and is herein designated as DNA59488-1603.



The full length clone shown in Figure 189 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 54-56 and ending at the stop codon found at nucleotide positions 909-911 (Figure 189; SEQ ID NO:271). The predicted polypeptide precursor (Figure 190, SEQ ID NO:272) is 285 amino acids long. PRO1360 has a calculated molecular weight of approximately 31,433 daltons and an estimated pI of approximately 7.32. Clone DNA59488-1603 was deposited with the ATCC on August 25, 1998 and is assigned ATCC deposit no. 203157.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 190 (SEQ ID NO:272), revealed sequence identity between the PRO1360 amino acid sequence and the following Dayhoff sequences: UN51\_CAEEL, YD4B\_SCHPO, AF000634\_1, GFO\_ZYMMO, YE1J\_SCHPO, D86566\_1, ZMGFO\_1, S76976, PPSA\_SYNY3, and CEF28B1\_4.

#### EXAMPLE 84: Isolation of cDNA clones Encoding Human PRO1029

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 18763. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57854.

In light of an observed sequence homology between the DNA57854 consensus sequence and an EST sequence encompassed within the Merck EST clone no. T98880, the Merck EST clone T98880 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 191 and is herein designated as DNA59493-1420.

Clone DNA59493-1420 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 39-41 and ending at the stop codon at nucleotide positions 297-299 (Figure 191). The predicted polypeptide precursor is 86 amino acids long (Figure 192). The full-length PRO1029 protein shown in Figure 192 has an estimated molecular weight of about 9,548 daltons and a pI of about 8.52. Analysis of the full-length PRO1029 sequence shown in Figure 192 (SEQ ID NO:274) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19, an amino acid block having homology to bacterial rhodopsins retinal binding site protein from about amino acid 50 to about amino acid 61, a prenyl group binding site from about amino acid 83 to about amino acid 86 and a potential N-glycosylation site from about amino acid 45 to about amino acid 48. Clone DNA59493-1420 has been deposited with ATCC on July 1, 1998 and is assigned ATCC deposit no. 203050,

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 192 (SEQ ID NO:274), evidenced significant

homology between the PRO1029 amino acid sequence and the following Dayhoff sequences: S66088, AF031815\_1, MM4A6L\_1, PSEIS52a-1, S17699 and P\_R63635.

**EXAMPLE 85: Isolation of cDNA clones Encoding Human PRO1139**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 4461. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57312.

The DNA57312 consensus sequence included a 172 nucleotides long public EST (T62095, Merck/University of Washington public database). This EST clone, identified herein as a putative protein coding sequence, was purchased from Merck, and sequenced to provide the coding sequence of PRO1139 (Figure 193). As noted before, the deduced amino acid sequence of DNA59497-1496 shows a significant sequence identity with the deduced amino acid sequence of HSOBRGRP\_1. The full-length protein (Figure 194) contains a putative signal peptide between amino acid residues 1 and about 28, and three putative transmembrane domains (approximate amino acid residues 33-52, 71-89, 98-120).

**EXAMPLE 86: Isolation of cDNA clones Encoding Human PRO1309**

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to SLIT.

RNA for construction of cDNA libraries was isolated from human fetal brain tissue. The cDNA libraries used to isolate the cDNA clones encoding human PRO1309 were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI.

The cDNA libraries (prepared as described above), were screened by hybridization with a synthetic oligonucleotide probe derived from the above described Incyte EST sequence:

5'-TCCGTGCAGGGGGACGCCTTTCAGAACTGCGCCGAGTTAAGGAAC-3' (SEQ ID NO:279).

A cDNA clone was isolated and sequenced in entirety. The entire nucleotide sequence of DNA59588-1571 is shown in Figure 195 (SEQ ID NO:277). Clone DNA59588-1571 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 720-722 and a stop codon at nucleotide positions 2286-2288 (Figure 195; SEQ ID NO:277). The predicted polypeptide precursor is 522 amino acids

long. The signal peptide is approximately at 1-34 and the transmembrane domain is at approximately 428-450 of SEQ ID NO:278. Clone DNA59588-1571 has been deposited with ATCC and is assigned ATCC deposit no. 203106. The full-length PRO1309 protein shown in Figure 196 has an estimated molecular weight of about 58,614 daltons and a pI of about 7.42.

5 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 196 (SEQ ID NO:278), revealed sequence identity between the PRO1309 amino acid sequence and the following Dayhoff sequences: AB007876\_1, GPV\_MOUSE, ALS\_RAT, P\_R85889, LUM\_CHICK, AB014462\_1, PGS1\_CANFA, CEM88\_7, A58532 and GEN11209.

EXAMPLE 87: Isolation of cDNA Clones Encoding Human PRO1028

10 Use of the signal sequence algorithm described in Example 3 above allowed identification of a certain EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in  
15 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA59603.

20 In light of an observed sequence homology between the DNA59603 sequence and an EST sequence contained within Incyte EST clone no. 1497725, the Incyte EST clone no. 1497725 was purchased and the cDNA insert was obtained and sequenced. It was found that the insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 197 and is herein designated as DNA59603-1419.

25 The entire nucleotide sequence of DNA59603-1419 is shown in Figure 197 (SEQ ID NO:280). Clone DNA59603-1419 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 21-23 and ending at the stop codon at nucleotide positions 612-614 (Figure 197). The predicted polypeptide precursor is 197 amino acids long (Figure 198). The full-length PRO1028 protein shown in Figure 198 has an estimated molecular weight of about 20,832 daltons and a pI of about 8.74. Clone DNA59603-1419 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

30 Analyzing the amino acid sequence of SEQ ID NO:281, the putative signal peptide is at about amino acids 1-19 of SEQ ID NO:281. An N-glycosylation site is at about amino acids 35-38 of SEQ ID NO:281. A C-type lectin domain is at about amino acids 108-117 of SEQ ID NO:281, indicating that PRO513 may be related to or be a lectin. The corresponding nucleotides of these amino acid sequences or others can be routinely determined given the sequences provided herein.



**EXAMPLE 88: Isolation of cDNA Clones Encoding Human PRO1027**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a certain EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56399.

In light of an observed sequence homology between the DNA56399 sequence and an EST sequence contained within Incyte EST clone no. 937605, the Incyte EST clone no. 937605 was purchased and the cDNA insert was obtained and sequenced. It was found that the insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 199 and is herein designated as DNA59605-1418.

The entire nucleotide sequence of DNA59605-1418 is shown in Figure 199 (SEQ ID NO:282). Clone DNA59605-1418 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 31-33 and ending at the stop codon at nucleotide positions 262-264 (Figure 199). The predicted polypeptide precursor is 77 amino acids long (Figure 200). The full-length PRO1027 protein shown in Figure 200 has an estimated molecular weight of about 8,772 daltons and a pI of about 9.62. Clone DNA59605-1418 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analyzing the amino acid sequence of SEQ ID NO:283, the putative signal peptide is at about amino acids 1-33 of SEQ ID NO:283. The type II fibronectin collagen-binding domain begins at about amino acid 30 of SEQ ID NO:283. The corresponding nucleotides for these amino acid sequences and others can be routinely determined given the sequences provided herein. PRO1027 may be involved in tissue formation or repair.

The following Dayhoff designations appear to have some sequence identity with PRO1027: SFT2\_YEAST; ATM3E9\_2; A69826; YM16\_MARPO; E64896; U60193\_2; MTLRAJ205\_1; MCU60315\_70; SPAS\_SHIFL; and S54213.

**EXAMPLE 89: Isolation of cDNA Clones Encoding Human PRO1107**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a certain EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence



obtained therefrom is herein designated DNA56402.

In light of an observed sequence homology between the DNA56402 sequence and an EST sequence contained within Incyte EST clone no. 3203694, the Incyte EST clone no. 3203694 was purchased and the cDNA insert was obtained and sequenced. It was found that the insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 201 and is herein designated as DNA59606-1471.

- 5 The entire nucleotide sequence of DNA59606-1471 is shown in Figure 201 (SEQ ID NO:284). Clone DNA59606-1471 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 244-246 and ending at the stop codon at nucleotide positions 1675-1677 of SEQ ID NO:284 (Figure 201). The predicted polypeptide precursor is 477 amino acids long (Figure 202). The full-length PRO1107 protein shown in Figure 202 has an estimated molecular weight of about 54,668 daltons and a pI of about 6.33.
- 10 Clone DNA59606-1471 has been deposited with ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

- Analysis of the amino acid sequence of the full-length PRO1107 polypeptide suggests that it possesses significant sequence similarity to phosphodiesterase I/nucleotide pyrophosphatase, human insulin receptor
- 15 tyrosine kinase inhibitor, alkaline phosphodiesterase and autotaxin, thereby indicating that PRO1107 may have at least one or all of the activities of these proteins, and that PRO1107 is a novel phosphodiesterase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO1107 amino acid sequence and at least the following Dayhoff sequences: AF005632\_1, P\_R79148, RNU78787\_1, AF060218\_4, A57080 and HUMATXT\_1.

20

EXAMPLE 90: Isolation of cDNA clones Encoding Human PRO1140

- Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence, Incyte cluster sequence No. 135917. This sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary
- 25 EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained
- 30 therefrom is herein designated DNA56416.

- In light of an observed sequence homology between DNA56416 and an EST sequence contained within Incyte EST clone no. 3345705, Incyte EST clone no. 3345705 was obtained and its insert sequenced. It was found that the insert encoded a full-length protein. The sequence, designated herein as DNA59607-1497, which is shown in Figure 203, is the full-length DNA sequence for PRO1140. Clone DNA59607-1497 was deposited
- 35 with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209946.

The entire nucleotide sequence of DNA59607-1497 is shown in Figure 203 (SEQ ID NO:286). Clone DNA59607-1497 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 210-212 and ending at the stop codon at nucleotide positions 975-977 (Figure 203). The predicted polypeptide precursor is 255 amino acids long (Figure 204). The full-length PRO1140 protein shown in Figure 204 has an estimated molecular weight of about 29,405 daltons and a pI of about 7.64. Analysis of the full-length PRO1140 sequence shown in Figure 204 (SEQ ID NO:287) evidences the presence of three transmembrane domains at about amino acids 101 to 118, 141 to 161 and 172 to 191.

5        Analysis of the amino acid sequence of the full-length PRO1140 polypeptide using the Dayhoff database (version 35.45 SwissProt 35) evidenced homology between the PRO1140 amino acid sequence and the following Dayhoff sequences: AF023602\_1, AF000368\_1, CIN3\_RAT, AF003373\_1, GEN13279, and AF003372\_1.

Clone DNA59607-1497 was deposited with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209946.

10

EXAMPLE 91: Isolation of cDNA clones Encoding Human PRO1106

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single Incyte EST sequence. This sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using  
15        the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, Univ. of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated  
20        DNA56423.

In light of an observed sequence homology between DNA56423 and an EST sequence contained within Incyte EST clone no. 1711247, Incyte EST clone no. 1711247 was obtained and its insert sequenced. It was found that the insert encoded a full-length protein. The sequence, designated herein as DNA59609-1470, which is shown in Figure 205, is the full-length DNA sequence for PRO1106. Clone DNA59609-1470 was deposited  
25        with the ATCC on June 9, 1998, and is assigned ATCC deposit no. 209963.

The entire nucleotide sequence of DNA59609-1470 is shown in Figure 205 (SEQ ID NO:288). Clone DNA59609-1470 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 61-63 and ending at the stop codon at nucleotide positions 1468-1470 of SEQ ID NO:288 (Figure 205). The predicted polypeptide precursor is 469 amino acids long (Figure 206). The full-length PRO1106 protein  
30        shown in Figure 206 has an estimated molecular weight of about 52,689 daltons and a pI of about 8.68. It is understood that the skilled artisan can construct the polypeptide or nucleic acid encoding therefor to exclude any one or more of all of these domains. For example, the transmembrane domain region(s) and/or either of the amino terminal or carboxyl end can be excluded. Clone DNA59609-1470 has been deposited with ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the  
35        sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO1106 polypeptide suggests that it possesses significant sequence similarity to the peroxisomal ca-dependent solute carrier, thereby indicating that PRO1106

may be a novel transporter. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO1106 amino acid sequence and at least the following Dayhoff sequences, AF004161\_1, IG002N01\_25, GDC\_BOVIN and BT1\_MAIZE.

**EXAMPLE 92: Isolation of cDNA clones Encoding Human PRO1291**

5 Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 120480. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul  
10 et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56425.

15 In light of an observed sequence homology between the DNA56425 sequence and an EST sequence encompassed within the Incyte EST clone no. 2798803, the Incyte EST clone 2798803 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 207 and is herein designated as DNA59610-1556.

20 Clone DNA59610-1556 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 61-63 and ending at the stop codon at nucleotide positions 907-909 (Figure 207). The predicted polypeptide precursor is 282 amino acids long (Figure 208). The full-length PRO1291 protein shown in Figure 208 has an estimated molecular weight of about 30,878 daltons and a pI of about 5.27. Analysis of the full-length PRO1291 sequence shown in Figure 208 (SEQ ID NO:291) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, a transmembrane domain from about amino acid 258 to about amino acid 281 and potential N-glycosylation sites from about amino acid 112 to about  
25 amino acid 115, from about amino acid 160 to about amino acid 163, from about amino acid 190 to about amino acid 193, from about amino acid 196 to about amino acid 199, from about amino acid 205 to about amino acid 208, from about amino acid 216 to about amino acid 219 and from about amino acid 220 to about amino acid 223.. Clone DNA59610-1556 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209990.

30 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 208 (SEQ ID NO:291), evidenced significant homology between the PRO1291 amino acid sequence and the following Dayhoff sequences: HSU90552\_1, HSU90144\_1, AF033107\_1, HSB73\_1, HSU90142\_1, GGCD80\_1, P\_W34452, MOG\_MOUSE, B39371 and P\_R71360.



**EXAMPLE 93: Isolation of cDNA clones Encoding Human PRO1105**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56430.

In light of an observed sequence homology between the DNA56430 sequence and an EST sequence encompassed within the Incyte EST clone no. 1853047, the Incyte EST clone 1853047 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 209 and is herein designated as DNA59612-1466.

The entire nucleotide sequence of DNA59612-1466 is shown in Figure 209 (SEQ ID NO:292). Clone DNA59612-1466 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 28-30 and ending at the stop codon at nucleotide positions 568-570 of SEQ ID NO:292 (Figure 209). The predicted polypeptide precursor is 180 amino acids long (Figure 210). The full-length PRO1105 protein shown in Figure 210 has an estimated molecular weight of about 20,040 daltons and a pI of about 8.35. Clone DNA59612-1466 has been deposited with the ATCC on June 9, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analyzing Figure 210, a signal peptide is at about amino acids 1-19 of SEQ ID NO:293 and transmembrane domains are shown at about amino acids 80-99 and 145-162 of SEQ ID NO:293. It is understood that the skilled artisan could form a polypeptide with all of or any combination or individual selection of these regions. It is also understood that the corresponding nucleic acids can be routinely identified and prepared based on the information provided herein.

**EXAMPLE 94: Isolation of cDNA clones Encoding Human PRO511**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56434.



In light of an observed sequence homology between the DNA56434 sequence and an EST sequence encompassed within the Incyte EST clone no. 1227491, the Incyte EST clone 1227491 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 211 and is herein designated as DNA59613-1417.

The entire nucleotide sequence of DNA59613-1417 is shown in Figure 211 (SEQ ID NO:294). Clone DNA59613-1417 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 233-235 and ending at the stop codon at nucleotide positions 944-946 (Figure 211). The predicted polypeptide precursor is 237 amino acids long (Figure 212). The full-length PRO511 protein shown in Figure 212 has an estimated molecular weight of about 25,284 daltons and a pI of about 5.74. Clone DNA59613-1417 has been deposited with the ATCC. Regarding the sequence, it is understood that the deposited clone contains the correct sequence, and the sequences provided herein are based on known sequencing techniques.

Analyzing the amino acid sequence of SEQ ID NO:295, the putative signal peptide is at about amino acids 1-25 of SEQ ID NO:295. The N-glycosylation sites are at about amino acids 45-48, 73-76, 107-110, 118-121, 132-135, 172-175, 175-178 and 185-188 of SEQ ID NO:295. An arthropod defensins conserved region is at about amino acids 176-182 of SEQ ID NO:295. A kringle domain begins at about amino acid 128 of SEQ ID NO:295 and a ly-6/u-PAR domain begins at about amino acid 6 of SEQ ID NO:295. The corresponding nucleotides of these amino acid sequences and others can be routinely determined given the sequences provided herein.

The designations appearing in a Dayhoff database with which PRO511 has some sequence identity are as follows: SSC20F10\_1; SF041083; P\_W26579; S44208; JC2394; PSTA\_DICDI; A27020; S59310; RAG1\_RABIT; and MUSBALBC1\_1.

#### EXAMPLE 95: Isolation of cDNA clones Encoding Human PRO1104

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56446.

In light of an observed sequence homology between the DNA56446 sequence and an EST sequence encompassed within the Incyte EST clone no. 2837496, the Incyte EST clone 2837496 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 213 and is herein designated as DNA59616-1465.

The entire nucleotide sequence of DNA59616-1465 is shown in Figure 213 (SEQ ID NO:296). Clone DNA59616-1465 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 109-111 and ending at the stop codon at nucleotide positions 1132-1134 of SEQ ID NO:296 (Figure 213). The predicted polypeptide precursor is 341 amino acids long (Figure 214). The full-length PRO1104 protein shown in Figure 214 has an estimated molecular weight of about 36,769 daltons and a pI of about 9.03. Clone DNA59616-1465 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analyzing Figure 214, a signal peptide is at about amino acids 1-22 of SEQ ID NO:297. N-myristoylation sites are at about amino acids 41-46, 110-115, 133-138, 167-172 and 179-184 of SEQ ID NO:297.

#### 10 EXAMPLE 96: Isolation of cDNA clones Encoding Human PRO1100

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In light of an observed sequence homology between the obtained consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2305379, the Incyte EST clone 2305379 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 215 and is herein designated as DNA59619-1464.

The entire nucleotide sequence of DNA59619-1464 is shown in Figure 215 (SEQ ID NO:298). Clone DNA59619-1464 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 33-35 and ending at the stop codon at nucleotide positions 993-995 of SEQ ID NO:298 (Figure 215). The predicted polypeptide precursor is 320 amino acids long (Figure 216). The full-length PRO1100 protein shown in Figure 216 has an estimated molecular weight of about 36,475 daltons and a pI of about 7.29. Clone DNA59619-1464 has been deposited with ATCC on July 1, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Upon analyzing SEQ ID NO:299, the approximate locations of the signal peptide, the transmembrane domains, an N-glycosylation site, an N-myristoylation site, a CUB domain and an amiloride-sensitive sodium channel domain are present. It is believed that PRO1100 may function as a channel. The corresponding nucleic acids for these amino acids and others can be routinely determined given SEQ ID NO:299..

**EXAMPLE 97: Isolation of cDNA clones Encoding Human PRO836**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (Lifeseq®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained is herein designated DNA56453.

In light of an observed sequence homology between the DNA56453 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2610075, the Incyte EST clone 2610075 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 217 and is herein designated as DNA59620-1463.

The entire nucleotide sequence of DNA59620-1463 is shown in Figure 217 (SEQ ID NO:300). Clone DNA59620-1463 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 65-67 and ending at the stop codon at nucleotide positions 1448-1450 of SEQ ID NO:300 (Figure 217). The predicted polypeptide precursor is 461 amino acids long (Figure 218). The full-length PRO836 protein shown in Figure 218 has an estimated molecular weight of about 52,085 daltons and a pI of about 5.36. Analysis of the full-length PRO836 sequence shown in Figure 218 (SEQ ID NO:301) evidences the presence of the following: a signal peptide, N-glycosylation sites, N-myristoylation sites, a domain conserved in the YJL126w/YLR351c/yhcX family of proteins, and a region having sequence identity with SLS1. Clone DNA59620-1463 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO836 polypeptide suggests that it possesses some sequence similarity to SLS1, thereby indicating that PRO836 may be involved in protein translocation of the ER. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced some homology between the PRO836 amino acid sequence and at least the following Dayhoff sequences, S58132, SPBC3B9\_1, S66714, CRU40057\_1 and IMA\_CAEEL.

**EXAMPLE 98: Isolation of cDNA clones Encoding Human PRO1141**

Use of the signal sequence algorithm described in Example 3 above allowed identification of an EST cluster sequence from the Incyte database, designated 11873. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or



in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56518.

In light of an observed sequence homology between the DNA56518 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2679995, the Incyte EST clone 2679995 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 219 and is herein designated as DNA59625-1498.

Clone DNA59625-1498 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 204-206 and ending at the stop codon at nucleotide positions 945-947 (Figure 219). The predicted polypeptide precursor is 247 amino acids long (Figure 220). The full-length PRO1141 protein shown in Figure 220 has an estimated molecular weight of about 26,840 daltons and a pI of about 8.19. Analysis of the full-length PRO1141 sequence shown in Figure 220 (SEQ ID NO:303) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19 and transmembrane domains from about amino acid 38 to about amino acid 57, from about amino acid 67 to about amino acid 83, from about amino acid 117 to about amino acid 139 and from about amino acid 153 to about amino acid 170. Clone DNA59625-1498 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209992.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 220 (SEQ ID NO:303), evidenced significant homology between the PRO1141 amino acid sequence and the following Dayhoff sequences: CEVF36H2L\_2, PCRB7PRJ\_1, AB000506\_1, LEU95008\_1, MRU87980\_15, YIGM\_ECOLI, STU65700\_1, GHU62778\_1, CYST\_SYNY3 and AF009567\_1.

#### EXAMPLE 99: Isolation of cDNA clones Encoding Human PRO1132

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA35934. Based on the DNA35934 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1132.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-TCCTGTGACCACCCCTCTAACACC-3' (SEQ ID NO:310) and  
reverse PCR primer: 5'-CTGGAACATCTGCTGCCAGATTTC-3' (SEQ ID NO:311).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus sequence which had the following nucleotide sequence:

5'-GTCGGATGACAGCAGCAGCCGCATCATCAATGGATCCGACTGCGATATGC-3' (SEQ ID NO:312).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1132 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal kidney.



DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1132 and the derived protein sequence for PRO1132.

The entire nucleotide sequence of PRO1132 is shown in Figure 225 (SEQ ID NO:308). Clone DNA59767-1489 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 354-356 and a stop codon at nucleotide positions 1233-1235 (Figure 225; SEQ ID NO:308). The predicted polypeptide precursor is 293 amino acids long. The signal peptide is at about amino acids 1-22 and the histidine active site is at about amino acids 104-109 of SEQ ID NO:309. Clone DNA59767-1489 has been deposited with ATCC (having the actual sequence rather than representations based on sequencing techniques as presented herein) and is assigned ATCC deposit no. 203108. The full-length PRO1132 protein shown in Figure 226 has an estimated molecular weight of about 32,020 daltons and a pI of about 8.7.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 226 (SEQ ID NO:309), revealed sequence identity between the PRO1132 amino acid sequence and the following Dayhoff sequences: SSU76256\_1, P\_W10694, MMAE000663\_6, AF013988\_1, U66061\_8, MMAE000665\_2, MMAE00066415, MMAE00066414, MMAE000665\_4 and MMAE00066412.

#### EXAMPLE 100: Isolation of cDNA clones Encoding Human NL7 (PRO1346)

A single EST sequence (#1398422) was found in the LIFESEQ<sup>®</sup> database as described in Example 1 above. This EST sequence was renamed as DNA45668. Based on the DNA45668 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for NL7.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-CACACGTCCAACCTCAATGGGCAG-3' (SEQ ID NO:315)

reverse PCR primer: 5'-GACCAGCAGGGCCAAGGACAAGG-3' (SEQ ID NO:316)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45668 sequence which had the following nucleotide sequence:

hybridization probe:

5'-GTTCTCTGAGATGAAGATCCGGCCGGTCCGGGAGTACCGCTTAG-3'

(SEQ ID NO:317)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the NL7 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from a human fetal kidney library (LIB227).

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for NL7 (designated herein as DNA59776-1600 [Figure 227, SEQ ID NO:313]) and the derived protein sequence for NL7 (PRO1346).

The entire coding sequence of NL7 (PRO1346) is shown in Figure 227 (SEQ ID NO:313). Clone DNA59776-1600 contains a single open reading frame with an apparent translational initiation site at nucleotide

positions 1-3 and an apparent stop codon at nucleotide positions 1384-1386. The predicted polypeptide precursor is 461 amino acids long. The protein contains an apparent type II transmembrane domain at amino acid positions from about 31 to about 50; fibrinogen beta and gamma chains C-terminal domain signature starting at about amino acid position 409, and a leucine zipper pattern starting at about amino acid positions 140, 147, 154 and 161, respectively. Clone DNA59776-1600 has been deposited with ATCC and is assigned ATCC deposit no. 203128. The full-length NL7 protein shown in Figure 228 has an estimated molecular weight of about 50,744 daltons and a pI of about 6.38.

Based on a WU-BLAST2 sequence alignment analysis (using the WU-BLAST2 computer program) of the full-length sequence, NL7 shows significant amino acid sequence identity to a human microfibril-associated glycoprotein (1 MFA4\_HUMAN); to known TIE-2 ligands and ligand homologues, ficolin, serum lectin and TGF-1 binding protein.

#### EXAMPLE 101: Isolation of cDNA clones Encoding Human PRO1131

A cDNA sequence isolated in the amylase screen described in Example 2 above is herein designated DNA43546 (see Figure 231; SEQ ID NO:320). The DNA43546 sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA45627.

Based on the DNA45627 sequence, oligonucleotide probes were generated and used to screen a human library prepared as described in paragraph 1 of Example 2 above. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

PCR primers (forward and 2 reverse) were synthesized:

forward PCR primer 5'-ATGCAGGCCAAGTACAGCAGCAC-3' (SEQ ID NO:321);

reverse PCR primer 1 5'-CATGCTGACGACTTCCTGCAAGC-3' (SEQ ID NO:322); and

reverse PCR primer 1 5'-CCACACAGTCTCTGCTTCTTGGG-3' (SEQ ID NO:323)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA45627 sequence which had the following nucleotide sequence:

hybridization probe

5'-ATGCTGGATGATGATGGGGACACCACCATGAGCCTGCATT-3' (SEQ ID NO:324).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1131 gene using the probe oligonucleotide and one of the PCR primers.

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 144-146, and a stop signal at nucleotide positions 984-986 (Figure 229; SEQ ID NO:318). The predicted polypeptide precursor is 280 amino acids long, has a calculated molecular weight of approximately 31,966 daltons and an estimated pI of approximately 6.26. The transmembrane domain sequence is at about 49-74 of SEQ ID NO:319 and the region having sequence identity with LDL receptors is about 50-265 of SEQ ID NO:319. PRO1131 contains potential N-linked glycosylation sites at amino acid positions 95-98 and 169-172 of SEQ ID NO:319. Clone DNA59777-1480 has been deposited with the ATCC and is assigned ATCC deposit no. 203111.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 230 (SEQ ID NO:319), evidenced some sequence identity between the PRO1131 amino acid sequence and the following Dayhoff sequences: AB010710\_1, I49053, I49115, RNU56863\_1, LY4A\_MOUSE, I55686, MMU56404\_1, I49361, AF030313\_1 and MMU09739\_1.

#### EXAMPLE 102: Isolation of cDNA clones Encoding Human PRO1281

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein as DNA35720. Based on the DNA35720 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1281.

PCR primers (forward and reverse) were synthesized:

##### forward PCR primers:

5'-TGGAAGGCTGCCGCAACGACAATC-3' (SEQ ID NO:327);  
5'-CTGATGTGGCCGATGTTCTG-3' (SEQ ID NO:328); and  
5'-ATGGCTCAGTGTGCAGACAG-3' (SEQ ID NO:329).

##### reverse PCR primers:

5'-GCATGCTGCTCCGTGAAGTAGTCC-3' (SEQ ID NO:330); and  
5'-ATGCATGGGAAAGAAGGCCTGCCC-3' (SEQ ID NO:331).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA35720 sequence which had the following nucleotide sequence:

##### hybridization probe:

5'-TGCACTGGTGACCACGAGGGGGTGCATATAGCCATCTGGAGCTGAG-3' (SEQ ID NO:332).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1281 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated human fetal liver.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1281 (designated herein as DNA59820-1549 [Figure 232, SEQ ID NO:325]; and the derived protein sequence for PRO1281.

The entire coding sequence of PRO1281 is shown in Figure 232 (SEQ ID NO:325). Clone DNA59820-1549 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 228-230 and an apparent stop codon at nucleotide positions 2553-2555. The predicted polypeptide precursor is 775 amino acids long. The full-length PRO1281 protein shown in Figure 233 has an estimated molecular weight of about 85,481 daltons and a pI of about 6.92. Additional features include a signal peptide at about amino acids 1-15; and potential N-glycosylation sites at about amino acids 138-141 and 361-364.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 233 (SEQ ID NO:326), revealed some sequence identity between the PRO1281 amino acid sequence and the following Dayhoff sequences: S44860, CET24D1\_1, CEC38H2\_3, CAC2\_HAECO, B3A2\_HUMAN, S22373, CEF38A3\_2, CEC34F6\_2, CEC34F6\_3, and CELT22B11\_3.

Clone DNA59820-1549 has been deposited with ATCC and is assigned ATCC deposit no. 203129.

#### EXAMPLE 103: Isolation of cDNA clones Encoding Human PRO1064

A cDNA sequence isolated in the amylase screen described in Example 2 above was found, by the WU-BLAST2 sequence alignment computer program, to have no significant sequence identity to any known human protein. This cDNA sequence is herein designated DNA45288. The DNA45288 sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence is herein designated DNA48609. Oligonucleotide primers based upon the DNA48609 sequence were then synthesized and employed to screen a human fetal kidney cDNA library which resulted in the identification of the DNA59827-1426 clone shown in Figure 234. The cloning vector was pRK5B (pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)), and the cDNA size cut was less than 2800 bp.

The oligonucleotide probes employed were as follows:

forward PCR primer 5'-CTGAGACCCTGCAGCACCATCTG-3' (SEQ ID NO:336)

reverse PCR primer 5'-GGTGCTTCTTGAGCCCCACTTAGC-3' (SEQ ID NO:337)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA48609 sequence which had the following nucleotide sequence

hybridization probe

5'-AATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCTGT-3' (SEQ ID NO:338)

A full length clone was identified that contained a single open reading frame with an apparent translational initiation site at nucleotide positions 532-534 and a stop signal at nucleotide positions 991-993 (Figure 234, SEQ ID NO:333). The predicted polypeptide precursor is 153 amino acids long, has a calculated



molecular weight of approximately 17,317 daltons and an estimated pI of approximately 5.17. Analysis of the full-length PRO1064 sequence shown in Figure 235 (SEQ ID NO:334) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 24, a transmembrane domain from about amino acid 89 to about amino acid 110, an indole-3-glycerol phosphate synthase homology block from about amino acid 74 to about amino acid 105 and a Myb DNA binding domain protein repeat protein homology block from about amino acid 114 to about amino acid 137. Clone DNA59827-1426 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203089.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 235 (SEQ ID NO:334), evidenced homology between the PRO1064 amino acid sequence and the following Dayhoff sequences: MMNP15PRO\_1, BP187PLYH\_1, CELF42G8\_4, MMU58888\_1, GEN14270, TUB8\_SOLTU, RCN\_MOUSE, HUMRBSY79\_1, SESENODA\_1 and A21467\_1.

#### EXAMPLE 104: Isolation of cDNA clones Encoding Human PRO1379

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein DNA45232. Based on the DNA45232 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1379.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-TGGACACCGTACCCTGGTATCTGC-3' (SEQ ID NO:341)  
reverse PCR primer 5'-CCAACTCTGAGGAGAGCAAGTGGC-3' (SEQ ID NO:342)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA45232 sequence which had the following nucleotide sequence:

hybridization probe

5'-TGTATGTGCACACCCTCACCATCACCTCCAAGGGCAAGGAGAAC-3' (SEQ ID NO:343).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1379 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated human fetal kidney tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1379 which is designated herein as DNA59828-1608 and shown in Figure 237 (SEQ ID NO:339); and the derived protein sequence for PRO1379 (SEQ ID NO:340).

The entire coding sequence of PRO1379 is shown in Figure 237 (SEQ ID NO:339). Clone DNA59828-1608 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 10-12 and an apparent stop codon at nucleotide positions 1732-1734. The predicted polypeptide precursor is 574 amino acids long. The full-length PRO1379 protein shown in Figure 238 has an estimated molecular weight of about 65,355 daltons and a pI of about 8.73. Additional features include a signal peptide at about amino acids

1-17 and potential N-glycosylation sites at about amino acids 160-163, 287-290, and 323-326.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 238 (SEQ ID NO:340), revealed some homology between the PRO1379 amino acid sequence and the following Dayhoff sequences: YHY8\_YEAST, AF040625\_1, HP714394\_1, and HIV18U45630\_1.

5 Clone DNA59828-1608 has been deposited with ATCC and is assigned ATCC deposit no. 203158.

**EXAMPLE 105: Isolation of cDNA Clones Encoding Human PRO844**

10 An expressed sequence tag (EST) DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed sequence identity with aLP. Based on the information and discoveries provided herein, the clone for this EST, Incyte clone no. 2657496 from a cancerous lung library was further examined.

DNA sequencing of the insert for this clone gave a sequence (herein designated as DNA59838-1462; SEQ ID NO:344) which includes the full-length DNA sequence for PRO844 and the derived protein sequence for PRO844.

15 The entire nucleotide sequence of DNA59838-1462 is shown in Figure 239 (SEQ ID NO:344). Clone DNA59838-1462 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 5-7 and ending at the stop codon at nucleotide positions 338-340 of SEQ ID NO:344 (Figure 239). The predicted polypeptide precursor is 111 amino acids long (Figure 240). The full-length PRO844 protein shown in Figure 240 has an estimated molecular weight of about 12,050 daltons and a pI of about 5.45. Clone  
20 UNQ544 DNA59838-1462 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO844 polypeptide suggests that it possesses significant sequence similarity to serine protease inhibitors, thereby indicating that PRO844 may be a novel  
25 proteinase inhibitor. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced significant homology between the PRO844 amino acid sequence and at least the following Dayhoff sequences, ALK1\_HUMAN, P\_P82403, P\_P82402, ELAF\_HUMAN and P\_P60950.

**EXAMPLE 106: Isolation of cDNA Clones Encoding Human PRO848**

30 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in  
35 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence

obtained therefrom is herein designated DNA55999.

In light of an observed sequence homology between the DNA55999 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2768571, the Incyte EST clone 2768571 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 241 and is herein designated as DNA59839-1461.

5 The entire nucleotide sequence of DNA59839-1461 is shown in Figure 241 (SEQ ID NO:346). Clone DNA59839-1461 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 146-148 and ending at the stop codon at nucleotide positions 1946-1948 of SEQ ID NO:346 (Figure 241). The predicted polypeptide precursor is 600 amino acids long (Figure 242). The full-length PRO848 protein shown in Figure 242 has an estimated molecular weight of about 68,536 daltons. Clone DNA59839-1461  
10 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analysis of the amino acid sequence of the full-length PRO848 polypeptide suggests that it may be a novel sialyltransferase. More specifically, an analysis of the Dayhoff database (version 35.45 SwissProt 35) evidenced sequence identity between the PRO848 amino acid sequence and at least the following Dayhoff  
15 sequences, P\_R78619 (GalNAc-alpha-2, 6-sialyltransferase), CAAG5\_CHICK (alpha-n-acetylgalactosamide alpha-2, 6-sialyltransferase), HSU14550\_1, CAG6\_HUMAN and P\_R63217 (human alpha-2, 3-sialyltransferase).

#### EXAMPLE 107: Isolation of cDNA Clones Encoding Human PRO1097

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single  
20 EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)  
25 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56006.

In light of an observed sequence homology between the DNA56006 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2408105, the Incyte EST clone 2408105 was purchased  
30 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 243 and is herein designated as DNA59841-1460.

The entire nucleotide sequence of DNA59841-1460 is shown in Figure 243 (SEQ ID NO:348). Clone DNA59841-1460 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 3-5 and ending at the stop codon at nucleotide positions 276-278 of SEQ ID NO:348 (Figure 243).  
35 The predicted polypeptide precursor is 91 amino acids long (Figure 244). The full-length PRO1097 protein shown in Figure 244 has an estimated molecular weight of about 10,542 daltons and a pI of about 10.04. Clone DNA59841-1460 has been deposited with ATCC on July 1, 1998. It is understood that the deposited clone has

the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

Analyzing Figure 244, the signal peptide is at about amino acids 1-20 of SEQ ID NO:349. The glycoprotease family protein domain starts at about amino acid 56, and the acyltransferase ChoActase/COT/CPT family peptide starts at about amino acid 49 of SEQ ID NO:349.

**EXAMPLE 108: Isolation of cDNA clones Encoding Human PRO1153**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56008.

In light of an observed sequence homology between the DNA56008 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2472409, the Incyte EST clone 2472409 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 245 and is herein designated as DNA59842-1502.

The full length clone shown in Figure 245 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 92-94 and ending at the stop codon found at nucleotide positions 683-685 (Figure 245; SEQ ID NO:350). The predicted polypeptide precursor (Figure 246, SEQ ID NO:351) is 197 amino acids long. PRO1153 has a calculated molecular weight of approximately 21,540 daltons and an estimated pI of approximately 8.31. Clone DNA59842-1502 has been deposited with ATCC and is assigned ATCC deposit no. 209982. It is understood that the correct and actual sequence is in the deposited clone while herein are present representations based on current sequencing techniques which may have minor errors.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1153 shows some amino acid sequence identity to the following Dayhoff designations: S57447; SOYHRGPC\_1; S46965; P\_P82971; VCPHEROPH\_1; EXTN\_TOBAC; MLCB2548\_9; ANXA\_RABIT; JC5437 and SSGP\_VOLCA.

**EXAMPLE 109: Isolation of cDNA clones Encoding Human PRO1154**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in



Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56025.

In light of an observed sequence homology between the DNA56025 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2169375, the Incyte EST clone 2169375 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 247 and is herein designated as DNA59846-1503.

The full length clone shown in Figure 247 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 86-88 and ending at the stop codon found at nucleotide positions 2909-2911 (Figure 247; SEQ ID NO:352). The predicted polypeptide precursor (Figure 248, SEQ ID NO:353) is 941 amino acids long. PRO1154 has a calculated molecular weight of approximately 107,144 daltons and an estimated pI of approximately 6.26. Clone DNA59846-1503 has been deposited with ATCC and is assigned ATCC deposit no. 209978.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1154 shows sequence identity to at least the following Dayhoff designations: AB011097\_1, AMPN\_HUMAN, RNU76997\_1, 159331, GEN14047, HSU62768\_1, P\_R51281, CET07F10\_1, SSU66371\_1, and AMPRE\_HUMAN.

#### EXAMPLE 110: Isolation of cDNA clones Encoding Human PRO1181

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database, designated herein as 82468. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56029.

In light of an observed sequence homology between the DNA56029 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2186536, the Incyte EST clone 2186536 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 249 and is herein designated as DNA59847-1511.

Clone DNA59847-1511 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 17-19 and ending at the stop codon at nucleotide positions 1328-1330 (Figure 249).

The predicted polypeptide precursor is 437 amino acids long (Figure 250). The full-length PRO1181 protein shown in Figure 250 has an estimated molecular weight of about 46,363 daltons and a pI of about 6.22. Analysis of the full-length PRO1181 sequence shown in Figure 250 (SEQ ID NO:355) evidences the presence of the

following: a signal peptide from about amino acid 1 to about amino acid 15, potential N-glycosylation sites from about amino acid 46 to about amino acid 49, from about amino acid 189 to about amino acid 192 and from about amino acid 382 to about amino acid 385 and amino acid sequence blocks having homology to Ly-6/u-PAR domain proteins from about amino acid 287 to about amino acid 300 and from about amino acid 98 to about amino acid 111. Clone DNA59847-1511 has been deposited with ATCC on August 4, 1998 and is assigned  
5 ATCC deposit no. 203098.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 250 (SEQ ID NO:355), evidenced homology between the PRO1181 amino acid sequence and the following Dayhoff sequences: AF041083\_1, P\_W26579, RNMAGPIAN\_1, CELT13C2\_2, LMSAP2GN\_1, S61882, CEF35C5\_12, DP87\_DICDI, GIU47631\_1 and  
10 P\_R07092.

**EXAMPLE 111: Isolation of cDNA clones Encoding Human PRO1182**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database, designated herein as 146647. This EST cluster sequence was  
15 then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and  
20 assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56033.

In light of an observed sequence homology between the DNA56033 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2595195, the Incyte EST clone 2595195 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.  
25 The sequence of this cDNA insert is shown in Figure 251 and is herein designated as DNA59848-1512.

Clone DNA59848-1512 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 67-69 and ending at the stop codon at nucleotide positions 880-882 (Figure 251). The predicted polypeptide precursor is 271 amino acids long (Figure 252). The full-length PRO1182 protein shown in Figure 252 has an estimated molecular weight of about 28,665 daltons and a pI of about 5.33. Analysis of  
30 the full-length PRO1182 sequence shown in Figure 252 (SEQ ID NO:357) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25, an amino acid block having homology to C-type lectin domain proteins from about amino acid 247 to about amino acid 256 and an amino acid sequence block having homology to C1q domain proteins from about amino acid 44 to about amino acid 77. Clone DNA59848-1512 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit  
35 no. 203088.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 252 (SEQ ID NO:357), evidenced significant

homology between the PRO1182 amino acid sequence and the following Dayhoff sequences: PSPD\_BOVIN, CL43\_BOVIN, CONG\_BOVIN, P\_W18780, P\_R45005, P\_R53257 and CELEGAP7\_1.

**EXAMPLE 112: Isolation of cDNA clones Encoding Human PRO1155**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single  
 5 EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of  
 expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary  
 EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The  
 homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in  
Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)  
 10 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with  
 the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence  
 obtained therefrom is herein designated DNA56102.

In light of an observed sequence homology between the DNA56102 consensus sequence and an EST  
 sequence encompassed within the Incyte EST clone no. 2858870, the Incyte EST clone 2858870 was purchased  
 15 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.  
 The sequence of this cDNA insert is shown in Figure 253 and is herein designated as DNA59849-1504.

The full length clone shown in Figure 253 contained a single open reading frame with an apparent  
 translational initiation site at nucleotide positions 158-160 and ending at the stop codon found at nucleotide  
 positions 563-565 (Figure 253; SEQ ID NO:358). The predicted polypeptide precursor (Figure 254, SEQ ID  
 20 NO:359) is 135 amino acids long. PRO1155 has a calculated molecular weight of approximately 14,833 daltons  
 and an estimated pI of approximately 9.78. Clone DNA59849-1504 has been deposited with ATCC and is  
 assigned ATCC deposit no. 209986. It is understood that the actual clone has the correct sequence whereas  
 herein are only representations which are prone to minor sequencing errors.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-  
 25 length sequence, PRO1155 shows some amino acid sequence identity with the following Dayhoff designations:  
 TKNK\_BOVIN; PVB19X587\_1; AF019049\_1; P\_W00948; S72864; P\_W00949; I62742; AF038501\_1;  
 TKNK\_HUMAN; and YAT1\_RHOBL. Based on the information provided herein, PRO1155 may play a role  
 in providing neuroprotection and cognitive enhancement.

**EXAMPLE 113: Isolation of cDNA clones Encoding Human PRO1156**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single  
 EST cluster sequence from the Incyte database, designated herein as 138851. This EST cluster sequence was  
 then compared to a variety of expressed sequence tag (EST) databases which included public EST databases  
 (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to  
 35 identify existing homologies. The homology search was performed using the computer program BLAST or  
 BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a  
 BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and



assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56261.

In light of an observed sequence homology between the DNA56261 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3675191, the Incyte EST clone 3675191 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

5 The sequence of this cDNA insert is shown in Figure 255 and is herein designated as DNA59853-1505.

The full length clone shown in Figure 255 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 212-214 and ending at the stop codon found at nucleotide positions 689-691 (Figure 255; SEQ ID NO:360). The predicted polypeptide precursor (Figure 256, SEQ ID NO:361) is 159 amino acids long. PRO1156 has a calculated molecular weight of approximately 17,476 daltons,  
10 an estimated pI of approximately 9.15, a signal peptide sequence at about amino acids 1 to about 22, and potential N-glycosylation sites at about amino acids 27-30 and 41-44.

Clone DNA59853-1505 was deposited with the ATCC on June 16, 1998 and is assigned ATCC deposit no. 209985.

15 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence shown in Figure 256 (SEQ ID NO:361), revealed some homology between the PRO1156 amino acid sequence and the following Dayhoff sequences: D45027\_1, P\_R79914, JC5309, KBF2\_HUMAN, AF010144\_1, GEN14351, S68681, P\_R79915, ZMTAC\_3, and HUMCPGO\_1.

#### 20 EXAMPLE 114: Isolation of cDNA Clones Encoding Human PRO1098

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The  
25 homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56377.

30 In light of an observed sequence homology between the DNA56377 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3050917, the Incyte EST clone 3050917 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 257 and is herein designated as DNA59854-1459.

The entire nucleotide sequence of DNA59854-1459 is shown in Figure 257 (SEQ ID NO:362). Clone  
35 DNA59854-1459 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon at nucleotide positions 292-294 of SEQ ID NO:362 (Figure 257). The predicted polypeptide precursor is 78 amino acids long (Figure 258). The full-length PRO1098 protein



shown in Figure 258 has an estimated molecular weight of about 8,396 daltons and a pI of about 7.66. Clone DNA59854-1459 has been deposited with ATCC on June 16, 1998. It is understood that the deposited clone has the actual nucleic acid sequence and that the sequences provided herein are based on known sequencing techniques.

5 Analyzing Figure 258, a signal peptide appears to be at about amino acids 1-19 of SEQ ID NO:363, an N-glycosylation site appears to be at about amino acids 37-40 of SEQ ID NO:363, and N-myristoylation sites appear to be at about 15-20, 19-24 and 60-65 of SEQ ID NO:363.

#### EXAMPLE 115: Isolation of cDNA clones Encoding Human PRO1127

10 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57959.

20 In light of an observed sequence homology between the DNA57959 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 685126, the Merck EST clone 685126 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 259 and is herein designated as DNA60283-1484.

25 The full length clone shown in Figure 259 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 126-128 and ending at the stop codon found at nucleotide positions 327-329 (Figure 259; SEQ ID NO:364). The predicted polypeptide precursor (Figure 260, SEQ ID NO:365) is 67 amino acids long including a signal peptide at about 1-29 of SEQ ID NO:365. PRO1127 has a calculated molecular weight of approximately 7,528 daltons and an estimated pI of approximately 4.95. Clone DNA60283-1484 was deposited with the ATCC on July 1, 1998 and is assigned ATCC deposit no. 203043. It is understood that the deposited clone has the actual sequence, whereas representations which may have minor sequencing errors are presented herein.

30 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 260 (SEQ ID NO:365), revealed some homology between the PRO1127 amino acid sequence and the following Dayhoff sequences: AF037218\_48, P\_W09638, HBA\_HETPO, S39821, KR2\_EBV, CET20D3\_8, HCU37630\_1, HS193B12\_10, S40012 and TRITUBC\_1.

**EXAMPLE 116: Isolation of cDNA clones Encoding Human PRO1126**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The

5 homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56250.

10 In light of an observed sequence homology between the DNA56250 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1437250, the Incyte EST clone 1437250 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 261 and is herein designated as DNA60615-1483.

15 Clone DNA60615-1483 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 110-112 and ending at the stop codon at nucleotide positions 1316-1318 (Figure 261). The predicted polypeptide precursor is 402 amino acids long (Figure 262). The full-length PRO1126 protein shown in Figure 262 has an estimated molecular weight of about 45,921 daltons and a pI of about 8.60. Analysis of the full-length PRO1126 sequence shown in Figure 262 (SEQ ID NO:367) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 25 and potential N-glycosylation sites

20 from about amino acid 66 to about amino acid 69, from about amino acid 138 to about amino acid 141 and from about amino acid 183 to about amino acid 186. Clone DNA60615-1483 has been deposited with ATCC on June 16, 1998 and is assigned ATCC deposit no. 209980.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 262 (SEQ ID NO:367), evidenced significant

25 homology between the PRO1126 amino acid sequence and the following Dayhoff sequences: I73636, NOMR\_HUMAN, MMUSMYOC3\_1, HS454G6\_1, P\_R98225, RNU78105\_1, RNU72487\_1, AF035301\_1, CEELC48E7\_4 and CEF11C3\_3.

**EXAMPLE 117: Isolation of cDNA clones Encoding Human PRO1125**

30 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in

35 Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence

obtained therefrom is herein designated DNA56540.

In light of an observed sequence homology between the DNA56540 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1486114, the Incyte EST clone 1486114 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 263 and is herein designated as DNA60615-1483.

5 The full length clone shown in Figure 263 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 47-49 and ending at the stop codon found at nucleotide positions 1388-1390 (Figure 263; SEQ ID NO:368). The predicted polypeptide precursor (Figure 264, SEQ ID NO:369) is 447 amino acids long. PRO1125 has a calculated molecular weight of approximately 49,798 daltons and an estimated pI of approximately 9.78. Clone DNA60619-1482 has been deposited with ATCC and is assigned  
10 ATCC deposit no. 209993. It is understood that the clone has the actual sequence and that the sequences herein are representations based on current techniques which may be prone to minor errors.

Based on a WU-BLAST2 sequence alignment analysis (using the ALIGN computer program) of the full-length sequence, PRO1125 shows some sequence identity with the following Dayhoff designations: RCO1\_NEUCR; S58306; PKWA\_THECU; S76086; P\_R85881; HET1\_PODAN; SPU92792\_1;  
15 APAF\_HUMAN; S76414 and S59317.

#### EXAMPLE 118: Isolation of cDNA clones Encoding Human PRO1186

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of  
20 expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with  
25 the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56748.

In light of an observed sequence homology between the DNA56748 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3476792, the Incyte EST clone 3476792 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.  
30 The sequence of this cDNA insert is shown in Figure 265 and is herein designated as DNA60621-1516.

The full length clone shown in Figure 265 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 91-93 and ending at the stop codon found at nucleotide positions 406-408 (Figure 265; SEQ ID NO:370). The predicted polypeptide precursor (Figure 266, SEQ ID NO:371) is 105 amino acids long. The signal peptide is at amino acids 1-19 of SEQ ID NO:371. PRO1186 has a  
35 calculated molecular weight of approximately 11,715 daltons and an estimated pI of approximately 9.05. Clone DNA60621-1516 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203091.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 266 (SEQ ID NO:371), revealed some sequence identity between the PRO1186 amino acid sequence and the following Dayhoff sequences: VPRA\_DENPO, LFE4\_CHICK, AF034208\_1, AF030433\_1, A55035, COL\_RABIT, CELB0507\_9, S67826\_1, S34665 and CRU73817\_1.

5

**EXAMPLE 119: Isolation of cDNA clones Encoding Human PRO1198**

An initial DNA sequence referred to herein as DNA52083 was identified using a yeast screen in a human umbilical vein endothelial cell cDNA library that preferentially represents the 5' ends of the primary cDNA clones. DNA52083 was compared to ESTs from public databases (e.g., GenBank), and a proprietary  
10 EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA), using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. The ESTs were clustered and assembled into a consensus DNA sequence using the computer program "phrap" (Phil Green, University of Washington, Seattle, Washington). One or more of the ESTs was obtained from human breast skin tissue biopsy. This consensus sequence is designated herein as DNA52780.

15

In light of an observed sequence homology between the DNA52780 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3852910, the Incyte EST clone 3852910 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 267 and is herein designated as DNA60622-1525.

20

The full length DNA60622-1525 clone shown in Figure 267 (SEQ ID NO:372) contained a single open reading frame with an apparent translational initiation site at nucleotide positions 54 to 56 and ending at the stop codon found at nucleotide positions 741 to 743. The predicted polypeptide precursor, which is shown in Figure 268 (SEQ ID NO:373), is 229 amino acids long. PRO1198 has a calculated molecular weight of approximately 25,764 daltons and an estimated pI of approximately 9.17. There is a signal peptide sequence at about amino acids 1 through 34. There is sequence identity with glycosyl hydrolases family 31 protein at about amino acids  
25 142 to about 175.

25

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 268 (SEQ ID NO:373), revealed some homology between the PRO1198 amino acid sequence and the following Dayhoff sequences: ATF6H11\_6, UCRI\_RAT, TOBSUP2NT\_1, RCUERF3\_1, AMU88186\_1, P\_W22485, S56579, AF040711\_1, DPP4\_PIG.

30

Clone DNA60622-1525 was been deposited with the ATCC on August 4, 1998, and is assigned ATCC deposit no. 203090.

**EXAMPLE 120: Isolation of cDNA clones Encoding Human PRO1158**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single  
35 EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The



homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57248.

5 In light of an observed sequence homology between the DNA57248 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2640776, the Incyte EST clone 2640776 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 269 and is herein designated as DNA60625-1507.

10 The full length clone shown in Figure 269 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 163 to 165 and ending at the stop codon found at nucleotide positions 532 to 534 (Figure 269; SEQ ID NO:374). The predicted polypeptide precursor (Figure 270, SEQ ID NO:375) is 123 amino acids long. PRO1158 has a calculated molecular weight of approximately 13,113 daltons and an estimated pI of approximately 8.53. Additional features include a signal peptide sequence at about amino acids 1-19, a transmembrane domain at about amino acids 56-80, and a potential N-glycosylation site at  
15 about amino acids 36-39. Clone DNA60625-1507 was deposited with the ATCC on June 16, 1998 and is assigned ATCC deposit no. 209975.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 270 (SEQ ID NO:375), revealed some homology between the PRO1158 amino acid sequence and the following Dayhoff sequences: ATAC00310510F18A8.10,  
20 P\_R85151, PHS2\_SOLTU, RNMHCIBAC\_1, RNA1FMHC\_1, I68771, RNRT1A10G\_1, PTPA\_HUMAN, HUMGACA\_1, and CHKPTPA\_1.

EXAMPLE 121: Isolation of cDNA clones Encoding Human PRO1159

25 Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90)  
30 or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57221.

In light of an observed sequence homology between the DNA57221 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 376776, the Incyte EST clone 376776 was purchased  
35 and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 271 and is herein designated as DNA60627-1508.

Clone DNA60627-1508 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 92-94 and ending at the stop codon at nucleotide positions 362-364 (Figure 271). The predicted polypeptide precursor is 90 amino acids long (Figure 272). The full-length PRO1159 protein shown in Figure 272 has an estimated molecular weight of about 9,840 daltons and a pI of about 10.13. Analysis of the full-length PRO1159 sequence shown in Figure 272 (SEQ ID NO:377) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 15 and a potential N-glycosylation site from about amino acid 38 to about amino acid 41. Clone DNA60627-1508 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203092.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 272 (SEQ ID NO:377), evidenced significant homology between the PRO1159 amino acid sequence and the following Dayhoff sequences: AF016494\_6, AF036708\_20, DSSCUTE\_1, D89100\_1, S28060, MEFA\_XENLA, AF020798\_12, G70065, E64423, JQ2005.

#### EXAMPLE 122: Isolation of cDNA clones Encoding Human PRO1124

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56035.

In light of an observed sequence homology between the DNA56035 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 2767646, the Incyte EST clone 2767646 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 273 and is herein designated as DNA60629-1481.

The full length clone shown in Figure 273 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 25-27 and ending at the stop codon found at nucleotide positions 2782-2784 (Figure 273; SEQ ID NO:378). The predicted polypeptide precursor (Figure 274, SEQ ID NO:379) is 919 amino acids long. PRO1124 has a calculated molecular weight of approximately 101,282 daltons and an estimated pI of approximately 5.37. Clone DNA60629-1481 has been deposited with the ATCC and is assigned ATCC deposit no. 209979. It is understood that the deposited clone has the actual sequence, whereas only representations based on current sequencing techniques which may include normal and minor errors, are provided herein.

Based on a WU-BLAST2 sequence alignment analysis of the full-length sequence, PRO1124 shows significant amino acid sequence identity to a chloride channel protein and to ECAM-1. Specifically, the following Dayhoff designations were identified as having sequence identity with PRO1124: ECLC\_BOVIN,

AF001261\_1, P\_W06548, SSC6A10\_1, AF004355\_1, S76691, AF017642, BYU06866\_2, CSA\_DICDI and SAU47139\_2.

**EXAMPLE 123: Isolation of cDNA clones Encoding Human PRO1287**

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and an EST was identified which showed homology to the fringe protein. This EST sequence was then compared to various EST databases including public EST databases (e.g., GenBank), and a proprietary EST database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify homologous EST sequences. The comparison was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)]. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). This consensus sequence obtained is herein designated DNA40568.

Based on the DNA40568 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1287. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et al., Current Protocols in Molecular Biology, *supra*, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CTCGGGGAAAGGGACTTGATGTTGG-3' (SEQ ID NO:382)

reverse PCR primer 1 5'-GCGAAGGTGAGCCTCTATCTCGTGCC-3' (SEQ ID NO:383)

reverse PCR primer 2 5'-CAGCCTACACGTATTGAGG-3' (SEQ ID NO:384)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40568 sequence which had the following nucleotide sequence

hybridization probe

5'-CAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTCCC-3' (SEQ ID NO:385).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pairs identified above. A positive library was then used to isolate clones encoding the PRO1287 gene using the probe oligonucleotide and one of the PCR primers.

RNA for construction of the cDNA libraries was isolated from human bone marrow tissue. The cDNA libraries used to isolated the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to Sall hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD;



pRK5B is a precursor of pRK5D that does not contain the SfiI site; see, Holmes et al., Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1287 (designated herein as DNA61755-1554 [Figure 275, SEQ ID NO:380]) and the derived protein sequence for PRO1287.

5       The entire nucleotide sequence of DNA61755-1554 is shown in Figure 275 (SEQ ID NO:380). The full length clone contained a single open reading frame with an apparent translational initiation site at nucleotide positions 655-657 and a stop signal at nucleotide positions 2251-2253 (Figure 275, SEQ ID NO:380). The predicted polypeptide precursor is 532 amino acids long, has a calculated molecular weight of approximately 61,351 daltons and an estimated pI of approximately 8.77. Analysis of the full-length PRO1287 sequence shown  
10 in Figure 276 (SEQ ID NO:381) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 27 and potential N-glycosylation sites from about amino acid 315 to about amino acid 318 and from about amino acid 324 to about amino acid 327. Clone DNA61755-1554 has been deposited with ATCC on August 11, 1998 and is assigned ATCC deposit no. 203112.

15       An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 276 (SEQ ID NO:381), evidenced significant homology between the PRO1287 amino acid sequence and the following Dayhoff sequences: CET24D1\_1, EZRI\_BOVIN, GGU19889\_1, CC3\_YEAST, S74244, NALS\_MOUSE, MOES\_PIG, S28660, S44860 and YNA4\_CAEEL.

#### 20    **EXAMPLE 124: Isolation of cDNA clones Encoding Human PRO1312**

DNA55773 was identified in a human fetal kidney cDNA library using a yeast screen that preferentially represents the 5' ends of the primary cDNA clones. Based on the DNA55773 sequence, oligonucleotides were synthesized for use as probes to isolate a clone of the full-length coding sequence for PRO1312.

25       The full length DNA61873-1574 clone shown in Figure 277 (SEQ ID NO:386) contained a single open reading frame with an apparent translational initiation site at nucleotide positions 7-9 and ending at the stop codon found at nucleotide positions 643-645. The predicted polypeptide precursor is 212 amino acids long (Figure 278, SEQ ID NO:387). PRO1312 has a calculated molecular weight of approximately 24,024 daltons and an estimated pI of approximately 6.26. Other features include a signal peptide at about amino acids 1-14; a transmembrane domain at about amino acids 141-160, and potential N-glycosylation sites at about amino acids  
30 76-79 and 93-96.

35       An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 278 (SEQ ID NO:387), revealed some homology between the PRO1312 amino acid sequence and the following Dayhoff sequences: GCINTALPH\_1, GIBMUC1A\_1, P\_R96298, AF001406\_1, PVU88874\_1, P\_R85151, AF041409\_1, CELC50F2\_7, C45875, and AB009510\_21.

Clone DNA61873-1574 has been deposited with ATCC and is assigned ATCC deposit no. 203132.



**EXAMPLE 125: Isolation of cDNA clones Encoding Human PRO1192**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is designated herein DNA35924. Based on the DNA35924 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1192.

PCR primers (forward and reverse) were synthesized:

forward PCR primer: 5'-CCGAGGCCATCTAGAGGCCAGAGC-3' (SEQ ID NO:390)

reverse PCR primer: 5'-ACAGGCAGAGCCAATGGCCAGAGC-3' (SEQ ID NO:391).

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA35924 sequence which had the following nucleotide sequence:

hybridization probe:

5'-GAGAGGACTGCGGGAGTTTGGGACCTTTGTGCAGACGTGCTCATG-3' (SEQ ID NO:392).

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1192 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver and spleen tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1192 designated herein as DNA62814-1521 and shown in Figure 279 (SEQ ID NO:388); and the derived protein sequence for PRO1192 which is shown in Figure 280 (SEQ ID NO:389).

The entire coding sequence of PRO1192 is shown in Figure 279 (SEQ ID NO:388). Clone DNA62814-1521 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and an apparent stop codon at nucleotide positions 766-768. The predicted polypeptide precursor is 215 amino acids long. The predicted polypeptide precursor has the following features: a signal peptide at about amino acids 1-21; a transmembrane domain at about amino acids 153-176; potential N-glycosylation sites at about amino acids 39-42 and 118-121; and homology with myelin P0 proteins at about amino acids 27-68 and 99-128 of Figure 280. The full-length PRO1192 protein shown in Figure 280 has an estimated molecular weight of about 24,484 daltons and a pI of about 6.98.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 280 (SEQ ID NO:389), revealed homology between the PRO1192 amino acid sequence and the following Dayhoff sequences: GEN12838, MYP0\_HUMAN, AF049498\_1, GEN14531, P\_W14146, HS46KDA\_1, CINB\_RAT, OX2G\_RAT, D87018\_1, and D86996\_2.

Clone DNA62814-1521 was deposited with the ATCC on August 4, 1998, and is assigned ATCC deposit no. 203093.

**EXAMPLE 126: Isolation of cDNA clones Encoding Human PRO1160**

A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA40650. Based on the DNA40650 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1160.

PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-GCTCCCTGATCTTCATGTCACCACC-3' (SEQ ID NO:395)

reverse PCR primer 5'-CAGGGACACACTCTACCATTCCGGGAG-3' (SEQ ID NO:396)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA40650 sequence which had the following nucleotide sequence

hybridization probe

5'-CCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTC-3' (SEQ ID NO:397)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1160 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human breast tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1160 (designated herein as DNA62872-1509 [Figure 281, SEQ ID NO: 393]) and the derived protein sequence for PRO1160.

The entire nucleotide sequence of DNA62872-1509 is shown in Figure 281 (SEQ ID NO:393). Clone DNA62872-1509 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 40-42 and ending at the stop codon at nucleotide positions 310-312 (Figure 281). The predicted polypeptide precursor is 90 amino acids long (Figure 282). The full-length PRO1160 protein shown in Figure 282 has an estimated molecular weight of about 9,039 daltons and a pI of about 4.37. Analysis of the full-length PRO1160 sequence shown in Figure 282 (SEQ ID NO:394) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19 and a protein kinase C phosphorylation site from about amino acid 68 to about amino acid 70. Clone DNA62872-1509 has been deposited with ATCC on August 4, 1998 and is assigned ATCC deposit no. 203100.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 282 (SEQ ID NO:394), evidenced significant homology between the PRO1160 amino acid sequence and the following Dayhoff sequences: B30305, GEN13490, I53641, S53363, HA34\_BRELC, SP96\_DICDI, S36326, SSU51197\_10, MUC1\_XENLA, TCU32448\_1 and AF000409\_1.

**EXAMPLE 127: Isolation of cDNA clones Encoding Human PRO1187**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of

expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57726.

In light of an observed sequence homology between the DNA57726 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 358563, the Incyte EST clone 358563 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

10 The sequence of this cDNA insert is shown in Figure 283 and is herein designated as DNA62876-1517.

The full length clone shown in Figure 283 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 121-123 and ending at the stop codon found at nucleotide positions 481-483 (Figure 283; SEQ ID NO:398). The predicted polypeptide precursor (Figure 284, SEQ ID NO:399) is 120 amino acids long. The signal peptide is at about amino acids 1-17 of SEQ ID NO:399. PRO1187 has a calculated molecular weight of approximately 12,925 daltons and an estimated pI of approximately 9.46. Clone DNA62876-1517 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203095. It is understood that the deposited clone contains the actual sequence and that the representations herein may have minor sequencing errors.

20 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 284 (SEQ ID NO:399), revealed some sequence identity (and therefore some relation) between the PRO1187 amino acid sequence and the following Dayhoff sequences: MGNENDOBX\_1, CELF41G3\_9, AMPG\_STRLI, HSBBOVHERL\_2, LEEXTEN10\_1, AF029958\_1 and P\_W04957.

#### 25 EXAMPLE 128: Isolation of cDNA clones Encoding Human PRO1185

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56426.

35 In light of an observed sequence homology between the DNA56426 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3284411, the Incyte EST clone 3284411 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein.

The sequence of this cDNA insert is shown in Figure 285 and is herein designated as DNA62881-1515.

The full length DNA62881-1515 clone shown in Figure 285 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 4-6 and ending at the stop codon found at nucleotide positions 598-600 (Figure 285; SEQ ID NO:400). The predicted polypeptide precursor (Figure 286, SEQ ID NO:401) is 198 amino acids long. The signal peptide is at about amino acids 1-21 of SEQ ID NO:401.

5 PRO1185 has a calculated molecular weight of approximately 22,105 daltons and an estimated pI of approximately 7.73. Clone DNA62881-1515 has been deposited with the ATCC and is assigned ATCC deposit no. 203096.

10 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 286 (SEQ ID NO:401), revealed some sequence identity between the PRO1185 amino acid sequence and the following Dayhoff sequences: TUP1\_YEAST, AF041382\_1, MAOM\_SOLTU, SPPBPHU9\_1,I41024, EPCPLCFail\_1, HSPLEC\_1, YKL4\_CAEEL, A44643, TGU65922\_1.

#### EXAMPLE 129: Isolation of cDNA clones Encoding Human PRO1345

15 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA47364. Based on the DNA47364 consensus sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1345.

20 PCR primers (forward and reverse) were synthesized:

forward PCR primer 5'-CCTGGTTATCCCCAGGAAGTCCGAC-3' (SEQ ID NO:404)

reverse PCR primer 5'-CTCTTGCTGCTGCGACAGGCCTC-3' (SEQ ID NO:405)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the consensus DNA47364 sequence which had the following nucleotide sequence

25 hybridization probe

5'-CGCCCTCCAAGACTATGGTAAAAGGAGCCTGCCAGGTGTCAATGAC-3' (SEQ ID NO:406)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1345 gene using the probe oligonucleotide and one of the PCR primers. RNA  
30 for construction of the cDNA libraries was isolated from human breast carcinoma tissue.

DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1345 (designated herein as DNA64852-1589 [Figure 287, SEQ ID NO:402]) and the derived protein sequence for PRO1345.

35 The entire nucleotide sequence of DNA64852-1589 is shown in Figure 287 (SEQ ID NO:402). Clone DNA64852-1589 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 7-9 or 34-36 and ending at the stop codon at nucleotide positions 625-627 (Figure 287). The predicted polypeptide precursor is 206 amino acids long (Figure 288). The full-length PRO1345 protein shown in Figure



288 has an estimated molecular weight of about 23,190 daltons and a pI of about 9.40. Analysis of the full-length PRO1345 sequence shown in Figure 288 (SEQ ID NO:403) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31 or from about amino acid 10 to about amino acid 31 and a C-type lectin domain signature sequence from about amino acid 176 to about amino acid 190. Clone DNA64852-1589 has been deposited with ATCC on August 18, 1998 and is assigned ATCC deposit no. 203127.

5 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 288 (SEQ ID NO:403), evidenced significant homology between the PRO1345 amino acid sequence and the following Dayhoff sequences: BTU22298\_1, TETN\_CARSP, TETN\_HUMAN, MABA\_RAT, S34198, P\_W13144, MACMBPA\_1, A46274, PSPD\_RAT AND P\_R32188.

#### 10 EXAMPLE 130: Isolation of cDNA clones Encoding Human PRO1245

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary  
15 EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence  
20 obtained therefrom is herein designated DNA56019.

In light of an observed sequence homology between the DNA56019 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 1327836, the Incyte EST clone 1327836 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 289 and is herein designated as DNA64884-1527.

25 The full length clone shown in Figure 289 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 79-81 and ending at the stop codon found at nucleotide positions 391-393 (Figure 289; SEQ ID NO:407). The predicted polypeptide precursor (Figure 290, SEQ ID NO:408) is 104 amino acids long, with a signal peptide sequence at about amino acid 1 to about amino acid 18. PRO1245 has a calculated molecular weight of approximately 10,100 daltons and an estimated pI of  
30 approximately 8.76.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 290 (SEQ ID NO:408), revealed some homology between the PRO1245 amino acid sequence and the following Dayhoff sequences: SYA\_THETH, GEN11167, MTV044\_4, AB011151\_1, RLAJ2750\_3, SNEIPTRA\_1, S63624, C28391, A37907, and S14064.

35 Clone DNA64884-1245 was deposited with the ATCC on August 25, 1998 and is assigned ATCC deposit no. 203155.

**EXAMPLE 131: Isolation of cDNA clones Encoding Human PRO1358**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In light of an observed sequence homology between the consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 88718, the Incyte EST clone 88718 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 291 and is herein designated as DNA64890-1612.

The full length clone shown in Figure 291 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 86 through 88 and ending at the stop codon found at nucleotide positions 1418 through 1420 (Figure 291; SEQ ID NO:409). The predicted polypeptide precursor (Figure 292, SEQ ID NO:410) is 444 amino acids long. The signal peptide is at about amino acids 1-18 of SEQ ID NO:410. PRO1358 has a calculated molecular weight of approximately 50,719 daltons and an estimated pI of approximately 8.82. Clone DNA64890-1612 was deposited with the ATCC on August 18, 1998 and is assigned ATCC deposit no. 203131.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 292 (SEQ ID NO:410), revealed sequence identity between the PRO1358 amino acid sequence and the following Dayhoff sequences: P\_W07607, AB000545\_1, AB000546\_1, A1AT\_RAT, AB015164\_1, P\_P50021, COTR\_CAVPO, and HAMHPP\_1. The variants claimed in this application exclude these sequences.

**EXAMPLE 132: Isolation of cDNA clones Encoding Human PRO1195**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA55716.

In light of an observed sequence homology between the DNA55716 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3252980, the Incyte EST clone 3252980 was purchased

and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 293 and is herein designated as DNA65412-1523.

The full length clone shown in Figure 293 contained a single open reading frame with an apparent translational initiation site at nucleotide positions 58-60 and ending at the stop codon found at nucleotide positions 511-513 (Figure 293; SEQ ID NO:411). The predicted polypeptide precursor (Figure 294, SEQ ID NO:412) is 151 amino acids long. The signal sequence is at about amino acids 1-22 of SEQ ID NO:412. PRO1195 has a calculated molecular weight of approximately 17,277 daltons and an estimated pI of approximately 5.33. Clone DNA65412-1523 was deposited with the ATCC on August 4, 1998 and is assigned ATCC deposit no. 203094.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 294 (SEQ ID NO:412), revealed some sequence identity between the PRO1195 amino acid sequence and the following Dayhoff sequences: MMU28486\_1, AF044205\_1, P\_W31186, CELK03C7\_1, F69034, EF1A\_METVA, AF024540\_1, SSU90353\_1, MRSP\_STAAU and P\_R97680.

#### EXAMPLE 133: Isolation of cDNA clones Encoding Human PRO1270

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57951.

In light of an observed sequence homology between the DNA57951 consensus sequence and an EST sequence encompassed within the Merck EST clone no. 124878, the Merck EST clone 124878 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 295 and is herein designated as DNA66308-1537.

Clone DNA66308-1537 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 103-105 and ending at the stop codon at nucleotide positions 1042-1044 (Figure 295).

The predicted polypeptide precursor is 313 amino acids long (Figure 296). The full-length PRO1270 protein shown in Figure 296 has an estimated molecular weight of about 34,978 daltons and a pI of about 5.71. Analysis of the full-length PRO1270 sequence shown in Figure 296 (SEQ ID NO:414) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 16, a potential N-glycosylation site from about amino acid 163 to about amino acid 166 and glycosaminoglycan attachment sites from about amino acid 74 to about amino acid 77 and from about amino acid 289 to about amino acid 292. Clone DNA66308-1537 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203159.



An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 296 (SEQ ID NO:414), evidenced significant homology between the PRO1270 amino acid sequence and the following Dayhoff sequences: XLU86699\_1, S49589, FIBA\_PARPA, FIBB\_HUMAN, P\_R47189, AF004326\_1, DRTENASCN\_1, AF004327\_1, P\_W01411 and FIBG\_BOVIN.

**EXAMPLE 134: Isolation of cDNA clones Encoding Human PRO1271**

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57955.

In light of an observed sequence homology between the DNA57955 consensus sequence and an EST sequence encompassed within the Merck EST clone no. AA625350, the Merck EST clone AA625350 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 297 and is herein designated as DNA66309-1538.

Clone DNA66309-1538 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 94-96 and ending at the stop codon at nucleotide positions 718-720 (Figure 297). The predicted polypeptide precursor is 208 amino acids long (Figure 298). The full-length PRO1271 protein shown in Figure 298 has an estimated molecular weight of about 21,531 daltons and a pI of about 8.99. Analysis of the full-length PRO1271 sequence shown in Figure 298 (SEQ ID NO:416) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 31 and a transmembrane domain from about amino acid 166 to about amino acid 187. Clone DNA66309-1538 has been deposited with ATCC on September 15, 1998 and is assigned ATCC deposit no. 203235.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 298 (SEQ ID NO:416), evidenced significant homology between the PRO1271 amino acid sequence and the following Dayhoff sequences: S57180, S63257, AGA1\_YEAST, BPU43599\_1, YS8A\_CAEEL, S67570, LSU54556\_2, S70305, VGLX\_HSVEB, and D88733\_1.

**EXAMPLE 135: Isolation of cDNA clones Encoding Human PRO1375**

A Merck/Wash. U. database was searched and a Merck EST was identified. This sequence was then put in a program which aligns it with other sequences from the Swiss-Prot public database, public EST databases (e.g., GenBank, Merck/Wash. U.), and a proprietary EST database (LIFESEQ®, Incyte



Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)] as a comparison of the extracellular domain (ECD) protein sequences to a 6 frame translation of the EST sequences. Those comparisons resulting in a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

A consensus DNA sequence was assembled relative to other EST sequences using phrap. This consensus sequence is designated herein "DNA67003".

Based on the DNA67003 consensus sequence, the nucleic acid (SEQ ID NO:417) was identified in a human pancreas library. DNA sequencing of the clone gave the full-length DNA sequence for PRO1375 and the derived protein sequence for PRO1375.

The entire coding sequence of PRO1375 is shown in Figure 299 (SEQ ID NO:417). Clone DNA67004-1614 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 104-106 and an apparent stop codon at nucleotide positions 698-700 of SEQ ID NO:417. The predicted polypeptide precursor is 198 amino acids long. The transmembrane domains are at about amino acids 11-28 (type II) and 103-125 of SEQ ID NO:418. Clone DNA67004-1614 has been deposited with ATCC and is assigned ATCC deposit no. 203115. The full-length PRO1375 protein shown in Figure 300 has an estimated molecular weight of about 22,531 daltons and a pI of about 8.47.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 300 (SEQ ID NO:418), revealed sequence identity between the PRO1375 amino acid sequence and the following Dayhoff sequences: AF026198\_5, CELR12C12\_5, S73465, Y011\_MYCPN, S64538\_1, P\_P8150, MUVSHPO10\_1, VSH\_MUMPL and CVU59751\_5.

#### EXAMPLE 136: Isolation of cDNA clones Encoding Human PRO1385

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA57952.

In light of an observed sequence homology between the DNA57952 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3129630, the Incyte EST clone 3129630 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 301 and is herein designated as DNA68869-1610.

Clone DNA68869-1610 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 26-28 and ending at the stop codon at nucleotide positions 410-412 (Figure 301). The predicted polypeptide precursor is 128 amino acids long (Figure 302). The full-length PRO1385 protein shown in Figure 302 has an estimated molecular weight of about 13,663 daltons and a pI of about 10.97. Analysis of the full-length PRO1385 sequence shown in Figure 302 (SEQ ID NO:420) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 28, and glycosylaminoglycan attachment sites from about amino acid 82 to about amino acid 85 and from about amino acid 91 to about amino acid 94. Clone DNA68869-1610 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203164.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 302 (SEQ ID NO:420), evidenced low homology between the PRO1385 amino acid sequence and the following Dayhoff sequences: CELT14A8\_1, LMNACHRA1\_1, HXD9\_HUMAN, CHKCMLF\_1, HS5PP34\_2, DMDRING\_1, A37107\_1, MMLUNGENE\_1, PUM\_DROME and DMU25117\_1.

#### 15 EXAMPLE 137: Isolation of cDNA clones Encoding Human PRO1387

Use of the signal sequence algorithm described in Example 3 above allowed identification of a single EST cluster sequence from the Incyte database. This EST cluster sequence was then compared to a variety of expressed sequence tag (EST) databases which included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) to identify existing homologies. The homology search was performed using the computer program BLAST or BLAST2 (Altschul et al., Methods in Enzymology 266:460-480 (1996)). Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into a consensus DNA sequence with the program "phrap" (Phil Green, University of Washington, Seattle, Washington). The consensus sequence obtained therefrom is herein designated DNA56259.

25 In light of an observed sequence homology between the DNA56259 consensus sequence and an EST sequence encompassed within the Incyte EST clone no. 3507924, the Incyte EST clone 3507924 was purchased and the cDNA insert was obtained and sequenced. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 303 and is herein designated as DNA68872-1620.

30 Clone DNA68872-1620 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 85-87 and ending at the stop codon at nucleotide positions 1267-1269 (Figure 303). The predicted polypeptide precursor is 394 amino acids long (Figure 304). The full-length PRO1387 protein shown in Figure 304 has an estimated molecular weight of about 44,339 daltons and a pI of about 7.10. Analysis of the full-length PRO1387 sequence shown in Figure 304 (SEQ ID NO:422) evidences the presence of the following: a signal peptide from about amino acid 1 to about amino acid 19, a transmembrane domain from about amino acid 275 to about amino acid 296, potential N-glycosylation sites from about amino acid 76 to about amino acid 79, from about amino acid 231 to about amino acid 234, from about amino acid 302 to about amino acid 305, from about amino acid 307 to about amino acid 310 and from about amino acid 376 to about amino acid

379, and amino acid sequence blocks having homology to myelin p0 protein from about amino acid 210 to about amino acid 239 and from about amino acid 92 to about amino acid 121. Clone DNA68872-1620 has been deposited with ATCC on August 25, 1998 and is assigned ATCC deposit no. 203160.

An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 304 (SEQ ID NO:422), evidenced significant homology between the PRO1387 amino acid sequence and the following Dayhoff sequences: P\_W36955, MYPO\_HETFR, HS46KDA\_1, AF049498\_1, MYO0\_HUMAN, AF030454\_1, A53268, SHPTCRA\_1, P\_W14146 and GEN12838.

#### EXAMPLE 138: Isolation of cDNA clones Encoding Human PRO1384

10 A consensus DNA sequence was assembled relative to other EST sequences using phrap as described in Example 1 above. This consensus sequence is herein designated DNA54192. Based on the DNA54192 sequence, oligonucleotides were synthesized: 1) to identify by PCR a cDNA library that contained the sequence of interest, and 2) for use as probes to isolate a clone of the full-length coding sequence for PRO1384.

PCR primers (forward and reverse) were synthesized:

15 forward PCR primer 5'-TGCAGCCCCTGTGACACAACTGG-3' (SEQ ID NO:425)

reverse PCR primer 5'-CTGAGATAACCGAGCCATCCTCCAC-3' (SEQ ID NO:426)

Additionally, a synthetic oligonucleotide hybridization probe was constructed from the DNA54192 sequence which had the following nucleotide sequence:

hybridization probe

20 5'-GGAGATAGCTGCTATGGGTTCTTCAGGCACAACTTAACATGGGAAG-3' (SEQ ID NO:427)

In order to screen several libraries for a source of a full-length clone, DNA from the libraries was screened by PCR amplification with the PCR primer pair identified above. A positive library was then used to isolate clones encoding the PRO1384 gene using the probe oligonucleotide and one of the PCR primers. RNA for construction of the cDNA libraries was isolated from human fetal liver.

25 DNA sequencing of the clones isolated as described above gave the full-length DNA sequence for PRO1384 (designated herein as DNA71159-1617 [Figure 305, SEQ ID NO:423]; and the derived protein sequence for PRO1384.

The entire coding sequence of PRO1384 is shown in Figure 305 (SEQ ID NO:423). Clone DNA71159-1617 contains a single open reading frame with an apparent translational initiation site at nucleotide positions 182-184 and an apparent stop codon at nucleotide positions 869-871. The predicted polypeptide precursor is 229 amino acids long. The full-length PRO1384 protein shown in Figure 306 has an estimated molecular weight of about 26,650 daltons and a pI of about 8.76. Additional features include a type II transmembrane domain at about amino acids 32-57, and potential N-glycosylation sites at about amino acids 68-71, 120-123, and 134-137.

35 An analysis of the Dayhoff database (version 35.45 SwissProt 35), using a WU-BLAST2 sequence alignment analysis of the full-length sequence shown in Figure 306 (SEQ ID NO:424), revealed homology between the PRO1384 amino acid sequence and the following Dayhoff sequences: AF054819\_1, HSAJ1687\_1, AF009511\_1, AB010710\_1, GEN13595, HSAJ673\_1, GEN13961, AB005900\_1, LECH\_CHICK, AF021349\_1,

and NK13\_RAT.

Clone DNA71159-1617 has been deposited with ATCC and is assigned ATCC deposit no. 203135.

**EXAMPLE 139: Use of PRO as a hybridization probe**

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

5 DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

10 Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

15

**EXAMPLE 140: Expression of PRO in *E. coli***

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli*.

20 The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., Gene, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode 25 for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

30 The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

35 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the



protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.71 g sodium citrate•2H<sub>2</sub>O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO<sub>4</sub>) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

*E. coli* paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin

from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

5 Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 141: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

10 The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called pRK5-PRO.

15 In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10  $\mu$ g pRK5-PRO DNA is mixed with about 1  $\mu$ g DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31:543 (1982)] and dissolved in 500  $\mu$ l of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M  $\text{CaCl}_2$ . To this mixture is added, dropwise, 500  $\mu$ l of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM  $\text{NaPO}_4$ , and a precipitate is allowed to form for 10 minutes at 25°C. The  
20 precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200  $\mu$ Ci/ml  $^{35}\text{S}$ -cysteine and 200  $\mu$ Ci/ml  $^{35}\text{S}$ -methionine. After  
25 a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate  
30 method described by Sompayrac et al., Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700  $\mu$ g pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5  $\mu$ g/ml bovine insulin and  
35 0.1  $\mu$ g/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as  $\text{CaPO}_4$  or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as  $^{35}\text{S}$ -methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by  $\text{Ni}^{2+}$ -chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect<sup>®</sup> (Quiagen), Dosper<sup>®</sup> or Fugene<sup>®</sup> (Boehringer Mannheim). The cells are grown as described in Lucas et al., *supra*. Approximately  $3 \times 10^7$  cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2  $\mu\text{m}$  filtered PS20 with 5% 0.2  $\mu\text{m}$  diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with  $3 \times 10^5$  cells/mL. The cell media is exchanged with fresh media by

centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at  $1.2 \times 10^6$  cells/mL. On day 0, the cell number pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22  $\mu$ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275  $\mu$ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

#### EXAMPLE 142: Expression of PRO in Yeast

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.



Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

5 **EXAMPLE 143: Expression of PRO in Baculovirus-Infected Insect Cells**

The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

15 Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

20 Expressed poly-his tagged PRO can then be purified, for example, by Ni<sup>2+</sup>-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl<sub>2</sub>; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm filter. A Ni<sup>2+</sup>-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A<sub>280</sub> with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A<sub>280</sub> baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni<sup>2+</sup>-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His<sub>10</sub>-tagged PRO are pooled and dialyzed against loading buffer.

35 Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

**EXAMPLE 144: Preparation of Antibodies that Bind PRO**

This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

5 Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with  
10 additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells  
15 are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of  
20 "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively,  
25 affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

**EXAMPLE 145: Purification of PRO Polypeptides Using Specific Antibodies**

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide  
30 is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.).  
35 Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody

is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

#### EXAMPLE 146: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (i) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the

solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

5

EXAMPLE 147: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

10

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

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It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

30

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

35



Deposit of Material

The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC):

<u>Table 2</u>		
	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
5	<u>Material</u>	
	DNA16422-1209	June 2, 1998
	DNA16435-1208	June 2, 1998
	DNA21624-1391	June 2, 1998
	DNA23334-1392	June 2, 1998
10	DNA26288-1239	April 21, 1998
	DNA26843-1389	August 4, 1998
	DNA26844-1394	June 2, 1998
	DNA30862-1396	June 2, 1998
	DNA35680-1212	April 21, 1998
15	DNA40621-1440	June 2, 1998
	DNA44161-1434	May 27, 1998
	DNA44694-1500	August 11, 1998
	DNA45495-1550	August 25, 1998
	DNA47361-1154	November 7, 1997
20	DNA47394-1572	August 11, 1998
	DNA48320-1433	May 27, 1998
	DNA48334-1435	June 2, 1998
	DNA48606-1479	July 1, 1998
	DNA49141-1431	June 23, 1998
25	DNA49142-1430	June 23, 1998
	DNA49143-1429	June 23, 1998
	DNA49647-1398	June 2, 1998
	DNA49819-1439	June 2, 1998
	DNA49820-1427	June 2, 1998
30	DNA49821-1562	June 16, 1998
	DNA52192-1369	July 1, 1998
	DNA52598-1518	August 11, 1998
	DNA53913-1490	August 25, 1998
	DNA53978-1443	June 16, 1998
35	DNA53996-1442	June 2, 1998
	DNA56041-1416	June 23, 1998
	DNA56047-1456	June 9, 1998
	DNA56050-1455	June 23, 1998
	DNA56110-1437	August 11, 1998
40	DNA56113-1378	July 1, 1998
	DNA56410-1414	June 2, 1998
	DNA56436-1448	May 27, 1998
	DNA56855-1447	June 23, 1998
	DNA56859-1445	June 23, 1998
45	DNA56860-1510	June 9, 1998
	DNA56865-1491	June 23, 1998
	DNA56866-1342	June 23, 1998
	DNA56868-1209	June 23, 1998
	DNA56869-1545	August 25, 1998
50	DNA56870-1492	June 2, 1998
	DNA57033-1403	May 27, 1998
	DNA57037-1444	May 27, 1998
	DNA57129-1413	June 16, 1998

	DNA57690-1374	209950	June 9, 1998
	DNA57693-1424	203008	June 23, 1998
	DNA57694-1341	203017	June 23, 1998
	DNA57695-1340	203006	June 23, 1998
	DNA57699-1412	203020	June 23, 1998
5	DNA57702-1476	209951	June 9, 1998
	DNA57704-1452	209953	June 9, 1998
	DNA57708-1411	203021	June 23, 1998
	DNA57710-1451	203048	July 1, 1998
	DNA57711-1501	203047	July 1, 1998
10	DNA57827-1493	203045	July 1, 1998
	DNA57834-1339	209954	June 9, 1998
	DNA57836-1338	203025	June 23, 1998
	DNA57838-1337	203014	June 23, 1998
	DNA57844-1410	203010	June 23, 1998
15	DNA58721-1475	203110	August 11, 1998
	DNA58723-1588	203133	August 18, 1998
	DNA58737-1473	203136	August 18, 1998
	DNA58743-1609	203154	August 25, 1998
	DNA58846-1409	209957	June 9, 1998
20	DNA58848-1472	209955	June 9, 1998
	DNA58849-1494	209958	June 9, 1998
	DNA58850-1495	209956	June 9, 1998
	DNA58853-1423	203016	June 23, 1998
	DNA58855-1422	203018	June 23, 1998
25	DNA59205-1421	203009	June 23, 1998
	DNA59211-1450	209960	June 9, 1998
	DNA59213-1487	209959	June 9, 1998
	DNA59214-1449	203046	July 1, 1998
	DNA59215-1425	209961	June 9, 1998
30	DNA59220-1514	209962	June 9, 1998
	DNA59488-1603	203157	August 25, 1998
	DNA59493-1420	203050	July 1, 1998
	DNA59497-1496	209941	June 4, 1998
	DNA59588-1571	203106	August 11, 1998
35	DNA59603-1419	209944	June 9, 1998
	DNA59605-1418	203005	June 23, 1998
	DNA59606-1471	209945	June 9, 1998
	DNA59607-1497	209957	June 9, 1998
	DNA59609-1470	209963	June 9, 1998
40	DNA59610-1559	209990	June 16, 1998
	DNA59612-1466	209947	June 9, 1998
	DNA59613-1417	203007	June 23, 1998
	DNA59616-1465	209991	June 16, 1998
	DNA59619-1464	203041	July 1, 1998
45	DNA59620-1463	209989	June 16, 1998
	DNA59625-1498	209992	June 17, 1998
	DNA59767-1489	203108	August 11, 1998
	DNA59776-1600	203128	August 18, 1998
	DNA59777-1480	203111	August 11, 1998
50	DNA59820-1549	203129	August 18, 1998
	DNA59827-1426	203089	August 4, 1998
	DNA59828-1608	203158	August 25, 1998
	DNA59838-1462	209976	June 16, 1998
	DNA59839-1461	209988	June 16, 1998
55	DNA59841-1460	203044	July 1, 1998
	DNA59842-1502	209982	June 16, 1998

	DNA59846-1503	209978	June 16, 1998
	DNA59847-1511	203098	August 4, 1998
	DNA59848-1512	203088	August 4, 1998
	DNA59849-1504	209986	June 16, 1998
	DNA59853-1505	209985	June 16, 1998
5	DNA59854-1459	209974	June 16, 1998
	DNA60283-1484	203043	July 1, 1998
	DNA60615-1483	209980	June 16, 1998
	DNA60619-1482	209993	June 16, 1998
	DNA60621-1516	203091	August 4, 1998
10	DNA60622-1525	203090	August 4, 1998
	DNA60625-1507	209975	June 16, 1998
	DNA60627-1508	203092	August 4, 1998
	DNA60629-1481	209979	June 16, 1998
	DNA61755-1554	203112	August 11, 1998
15	DNA61873-1574	203132	August 18, 1998
	DNA62814-1521	203093	August 4, 1998
	DNA62872-1509	203100	August 4, 1998
	DNA62876-1517	203095	August 4, 1998
	DNA62881-1515	203096	August 4, 1998
20	DNA64852-1589	203127	August 18, 1998
	DNA64884-1527	203155	August 25, 1998
	DNA64890-1612	203131	August 18, 1998
	DNA65412-1523	203094	August 4, 1998
	DNA66308-1537	203159	August 25, 1998
25	DNA66309-1538	203235	September 15, 1998
	DNA67004-1614	203115	August 11, 1998
	DNA68869-1610	203164	August 25, 1998
	DNA68872-1620	203160	August 25, 1998
30	DNA71159-1617	203135	August 18, 1998

These deposit were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the

deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition  
5 to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.



**WHAT IS CLAIMED IS:**

1. Isolated nucleic acid having at least 80% sequence identity to a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68 (SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ

ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422) and Figure 306 (SEQ ID NO:424).

2. The nucleic acid sequence of Claim 1, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of the sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372),

Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) and Figure 305 (SEQ ID NO:423).

3. The nucleic acid of Claim 1, wherein said nucleotide sequence comprises a nucleotide sequence selected from the group consisting of the full-length coding sequence of the sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID

NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) or Figure 305 (SEQ ID NO:423).

10           4.       Isolated nucleic acid which comprises the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 2.

5           5.       A vector comprising the nucleic acid of Claim 1.

15           6.       The vector of Claim 5 operably linked to control sequences recognized by a host cell transformed with the vector.

7.       A host cell comprising the vector of Claim 5.

20           8.       The host cell of Claim 7 wherein said cell is a CHO cell.

9.       The host cell of Claim 7 wherein said cell is an *E. coli*.

10.       The host cell of Claim 7 wherein said cell is a yeast cell.

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11.       A process for producing a PRO polypeptides comprising culturing the host cell of Claim 7 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

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12.       Isolated PRO polypeptide having at least 80% sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:6), Figure 6 (SEQ ID NO:8), Figure 9 (SEQ ID NO:14), Figure 12 (SEQ ID NO:20), Figure 15 (SEQ ID NO:23), Figure 18 (SEQ ID NO:28), Figure 20 (SEQ ID NO:30), Figure 23 (SEQ ID NO:33), Figure 25 (SEQ ID NO:36), Figure 27 (SEQ ID NO:41), Figure 30 (SEQ ID NO:47), Figure 32 (SEQ ID NO:52), Figure 34 (SEQ ID NO:57), Figure 36 (SEQ ID NO:62), Figure 38 (SEQ ID NO:67), Figure 41 (SEQ ID NO:73), Figure 47 (SEQ ID NO:84), Figure 49 (SEQ ID NO:95), Figure 51 (SEQ ID NO:97), Figure 53 (SEQ ID NO:99), Figure 57 (SEQ ID NO:103), Figure 64 (SEQ ID NO:113), Figure 66 (SEQ ID NO:115), Figure 68

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(SEQ ID NO:117), Figure 70 (SEQ ID NO:119), Figure 72 (SEQ ID NO:124), Figure 74 (SEQ ID NO:129), Figure 76 (SEQ ID NO:135), Figure 79 (SEQ ID NO:138), Figure 83 (SEQ ID NO:146), Figure 85 (SEQ ID NO:148), Figure 88 (SEQ ID NO:151), Figure 90 (SEQ ID NO:153), Figure 93 (SEQ ID NO:156), Figure 95 (SEQ ID NO:158), Figure 97 (SEQ ID NO:160), Figure 99 (SEQ ID NO:165), Figure 101 (SEQ ID NO:167), Figure 103 (SEQ ID NO:169), Figure 105 (SEQ ID NO:171), Figure 109 (SEQ ID NO:175), Figure 111 (SEQ ID NO:177), Figure 113 (SEQ ID NO:179), Figure 115 (SEQ ID NO:181), Figure 117 (SEQ ID NO:183), Figure 120 (SEQ ID NO:189), Figure 122 (SEQ ID NO:194), Figure 125 (SEQ ID NO:197), Figure 127 (SEQ ID NO:199), Figure 129 (SEQ ID NO:201), Figure 131 (SEQ ID NO:203), Figure 133 (SEQ ID NO:205), Figure 135 (SEQ ID NO:207), Figure 137 (SEQ ID NO:209), Figure 139 (SEQ ID NO:211), Figure 141 (SEQ ID NO:213), Figure 144 (SEQ ID NO:216), Figure 147 (SEQ ID NO:219), Figure 149 (SEQ ID NO:221), Figure 151 (SEQ ID NO:223), Figure 153 (SEQ ID NO:225), Figure 155 (SEQ ID NO:227), Figure 157 (SEQ ID NO:229), Figure 159 (SEQ ID NO:231), Figure 161 (SEQ ID NO:236), Figure 163 (SEQ ID NO:241), Figure 165 (SEQ ID NO:246), Figure 167 (SEQ ID NO:248), Figure 169 (SEQ ID NO:250), Figure 171 (SEQ ID NO:253), Figure 174 (SEQ ID NO:256), Figure 176 (SEQ ID NO:258), Figure 178 (SEQ ID NO:260), Figure 180 (SEQ ID NO:262), Figure 182 (SEQ ID NO:264), Figure 184 (SEQ ID NO:266), Figure 186 (SEQ ID NO:268), Figure 188 (SEQ ID NO:270), Figure 190 (SEQ ID NO:272), Figure 192 (SEQ ID NO:274), Figure 194 (SEQ ID NO:276), Figure 196 (SEQ ID NO:278), Figure 198 (SEQ ID NO:281), Figure 200 (SEQ ID NO:283), Figure 202 (SEQ ID NO:285), Figure 204 (SEQ ID NO:287), Figure 206 (SEQ ID NO:289), Figure 208 (SEQ ID NO:291), Figure 210 (SEQ ID NO:293), Figure 212 (SEQ ID NO:295), Figure 214 (SEQ ID NO:297), Figure 216 (SEQ ID NO:299), Figure 218 (SEQ ID NO:301), Figure 220 (SEQ ID NO:303), Figure 226 (SEQ ID NO:309), Figure 228 (SEQ ID NO:314), Figure 230 (SEQ ID NO:319), Figure 233 (SEQ ID NO:326), Figure 235 (SEQ ID NO:334), Figure 238 (SEQ ID NO:340), Figure 240 (SEQ ID NO:345), Figure 242 (SEQ ID NO:347), Figure 244 (SEQ ID NO:349), Figure 246 (SEQ ID NO:351), Figure 248 (SEQ ID NO:353), Figure 250 (SEQ ID NO:355), Figure 252 (SEQ ID NO:357), Figure 254 (SEQ ID NO:359), Figure 256 (SEQ ID NO:361), Figure 258 (SEQ ID NO:363), Figure 260 (SEQ ID NO:365), Figure 262 (SEQ ID NO:367), Figure 264 (SEQ ID NO:369), Figure 266 (SEQ ID NO:371), Figure 268 (SEQ ID NO:373), Figure 270 (SEQ ID NO:375), Figure 272 (SEQ ID NO:377), Figure 274 (SEQ ID NO:379), Figure 276 (SEQ ID NO:381), Figure 278 (SEQ ID NO:387), Figure 280 (SEQ ID NO:389), Figure 282 (SEQ ID NO:394), Figure 284 (SEQ ID NO:399), Figure 286 (SEQ ID NO:401), Figure 288 (SEQ ID NO:403), Figure 290 (SEQ ID NO:408), Figure 292 (SEQ ID NO:410), Figure 294 (SEQ ID NO:412), Figure 296 (SEQ ID NO:414), Figure 298 (SEQ ID NO:416), Figure 300 (SEQ ID NO:418), Figure 302 (SEQ ID NO:420), Figure 304 (SEQ ID NO:422) and Figure 306 (SEQ ID NO:424).

13. Isolated PRO polypeptide having at least 80% sequence identity to the amino acid sequence encoded by a nucleic acid molecule deposited under any ATCC accession number shown in Table 2.

14. A chimeric molecule comprising a polypeptide according to Claim 12 fused to a heterologous amino acid sequence.

15. The chimeric molecule of Claim 14 wherein said heterologous amino acid sequence is an epitope tag sequence.

16. The chimeric molecule of Claim 14 wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

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17. An antibody which specifically binds to a PRO polypeptide according to Claim 12.

18. The antibody of Claim 17 wherein said antibody is a monoclonal antibody.

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19. The antibody of Claim 17 wherein said antibody is a humanized antibody.

20. The antibody of Claim 17 wherein said antibody is an antibody fragment.

21. An isolated nucleic acid molecule which has at least 80% sequence identity to a nucleic acid which comprises a nucleotide sequence selected from the group consisting of that shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure

191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) and Figure 305 (SEQ ID NO:423).

22. An isolated nucleic acid molecule which has at least 80% sequence identity to the full-length coding sequence of a nucleotide sequence selected from the group consisting of that shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:5), Figure 5 (SEQ ID NO:7), Figure 8 (SEQ ID NO:13), Figure 11 (SEQ ID NO:19), Figure 14 (SEQ ID NO:22), Figure 17 (SEQ ID NO:27), Figure 19 (SEQ ID NO:29), Figure 22 (SEQ ID NO:32), Figure 24 (SEQ ID NO:35), Figure 26 (SEQ ID NO:40), Figure 29 (SEQ ID NO:46), Figure 31 (SEQ ID NO:51), Figure 33 (SEQ ID NO:56), Figure 35 (SEQ ID NO:61), Figure 37 (SEQ ID NO:66), Figure 40 (SEQ ID NO:72), Figure 46 (SEQ ID NO:83), Figure 48 (SEQ ID NO:94), Figure 50 (SEQ ID NO:96), Figure 52 (SEQ ID NO:98), Figure 56 (SEQ ID NO:102), Figure 63 (SEQ ID NO:112), Figure 65 (SEQ ID NO:114), Figure 67 (SEQ ID NO:116), Figure 69 (SEQ ID NO:118), Figure 71 (SEQ ID NO:123), Figure 73 (SEQ ID NO:128), Figure 75 (SEQ ID NO:134), Figure 78 (SEQ ID NO:137), Figure 82 (SEQ ID NO:145), Figure 84 (SEQ ID NO:147), Figure 87 (SEQ ID NO:150), Figure 89 (SEQ ID NO:152), Figure 92 (SEQ ID NO:155), Figure 94 (SEQ ID NO:157), Figure 96 (SEQ ID NO:159), Figure 98 (SEQ ID NO:164), Figure 100 (SEQ ID NO:166), Figure 102 (SEQ ID NO:168), Figure 104 (SEQ ID NO:170), Figure 108 (SEQ ID NO:174), Figure 110 (SEQ ID NO:176), Figure 112 (SEQ ID NO:178), Figure 114 (SEQ ID NO:180), Figure 116 (SEQ ID NO:182), Figure 119 (SEQ ID NO:188), Figure 121 (SEQ ID NO:193), Figure 124 (SEQ ID NO:196), Figure 126 (SEQ ID NO:198), Figure 128 (SEQ ID NO:200), Figure 130 (SEQ ID NO:202), Figure 132 (SEQ ID NO:204), Figure 134 (SEQ ID NO:206), Figure 136 (SEQ ID NO:208), Figure 138 (SEQ ID NO:210), Figure 140 (SEQ ID NO:212), Figure 143 (SEQ ID NO:215), Figure 146 (SEQ ID NO:218), Figure 148 (SEQ ID NO:220), Figure 150 (SEQ ID NO:222), Figure 152 (SEQ ID NO:224), Figure 154 (SEQ ID NO:226), Figure 156 (SEQ ID NO:228), Figure 158 (SEQ ID NO:230), Figure 160 (SEQ ID NO:235), Figure 162 (SEQ ID NO:240), Figure 164 (SEQ ID NO:245), Figure 166 (SEQ ID NO:247), Figure 168 (SEQ ID

NO:249), Figure 170 (SEQ ID NO:252), Figure 173 (SEQ ID NO:255), Figure 175 (SEQ ID NO:257), Figure 177 (SEQ ID NO:259), Figure 179 (SEQ ID NO:261), Figure 181 (SEQ ID NO:263), Figure 183 (SEQ ID NO:265), Figure 185 (SEQ ID NO:267), Figure 187 (SEQ ID NO:269), Figure 189 (SEQ ID NO:271), Figure 191 (SEQ ID NO:273), Figure 193 (SEQ ID NO:275), Figure 195 (SEQ ID NO:277), Figure 197 (SEQ ID NO:280), Figure 199 (SEQ ID NO:282), Figure 201 (SEQ ID NO:284), Figure 203 (SEQ ID NO:286), Figure 205 (SEQ ID NO:288), Figure 207 (SEQ ID NO:290), Figure 209 (SEQ ID NO:292), Figure 211 (SEQ ID NO:294), Figure 213 (SEQ ID NO:296), Figure 215 (SEQ ID NO:298), Figure 217 (SEQ ID NO:300), Figure 219 (SEQ ID NO:302), Figure 225 (SEQ ID NO:308), Figure 227 (SEQ ID NO:313), Figure 229 (SEQ ID NO:318), Figure 232 (SEQ ID NO:325), Figure 234 (SEQ ID NO:333), Figure 237 (SEQ ID NO:339), Figure 239 (SEQ ID NO:344), Figure 241 (SEQ ID NO:346), Figure 243 (SEQ ID NO:348), Figure 245 (SEQ ID NO:350), Figure 247 (SEQ ID NO:352), Figure 249 (SEQ ID NO:354), Figure 251 (SEQ ID NO:356), Figure 253 (SEQ ID NO:358), Figure 255 (SEQ ID NO:360), Figure 257 (SEQ ID NO:362), Figure 259 (SEQ ID NO:364), Figure 261 (SEQ ID NO:366), Figure 263 (SEQ ID NO:368), Figure 265 (SEQ ID NO:370), Figure 267 (SEQ ID NO:372), Figure 269 (SEQ ID NO:374), Figure 271 (SEQ ID NO:376), Figure 273 (SEQ ID NO:378), Figure 275 (SEQ ID NO:380), Figure 277 (SEQ ID NO:386), Figure 279 (SEQ ID NO:388), Figure 281 (SEQ ID NO:393), Figure 283 (SEQ ID NO:398), Figure 285 (SEQ ID NO:400), Figure 287 (SEQ ID NO:402), Figure 289 (SEQ ID NO:407), Figure 291 (SEQ ID NO:409), Figure 293 (SEQ ID NO:411), Figure 295 (SEQ ID NO:413), Figure 297 (SEQ ID NO:415), Figure 299 (SEQ ID NO:417), Figure 301 (SEQ ID NO:419), Figure 303 (SEQ ID NO:421) and Figure 305 (SEQ ID NO:423).

- 20           23.     An isolated extracellular domain of of PRO polypeptide.
24.     An isolated PRO polypeptide lacking its associated signal peptide.
25.     An isolated polypeptide having at least about 80% amino acid sequence identity to an
- 25   extracellular domain of of PRO polypeptide.
26.     An isolated polypeptide having at least about 80% amino acid sequence identity to a PRO
- polypeptide lacking its associated signal peptide.



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**FIGURE 1**

CGGACGCGTGGGTGCGAGGCCGAAGGTGACCGGGGACCGAGCATTTTCAGATCTGCTCGGTAGA  
CCTGGTGCACCACCACCATGTTGGCTGCAAGGCTGGTGTGTCTCCGGACACTACCTTCTAGG  
GTTTTCCACCCAGCTTTCACCAAGGCCTCCCCTGTTGTGAAGAATTCCATCACGAAGAATCA  
ATGGCTGTTAACACCTAGCAGGGAATATGCCACCAAAACAAGAATTGGGATCCGGCGTGGGA  
GAACTGGCCAAGAACTCAAAGAGGCAGCATTGGAACCATCGATGGAAAAAATATTTAAAATT  
GATCAGATGGGAAGATGGTTTGTGCTGGAGGGGCTGCTGTTGGTCTTGGAGCATTGTGCTA  
CTATGGCTTGGGACTGTCTAATGAGATTGGAGCTATTGAAAAGGCTGTAATTTGGCCTCAGT  
ATGTCAAGGATAGAATTCATTCCACCTATATGTACTTAGCAGGGAGTATTGGTTTAAACAGCT  
TTGTCTGCCATAGCAATCAGCAGAACGCCTGTTCTCATGAACTTCATGATGAGAGGCTCTTG  
GGTGACAATTGGTGTGACCTTTGCAGCCATGGTTGGAGCTGGAATGCTGGTACGATCAATAC  
CATATGACCAGAGCCCAGGCCCAAAGCATCTTGCTTGGTTGCTACATTCTGGTGTGATGGGT  
GCAGTGGTGGCTCCTCTGACAATATTAGGGGGTCCTCTTCTCATCAGAGCTGCATGGTACAC  
AGCTGGCATTGTGGGAGGCCTCTCCACTGTGGCCATGTGTGCGCCCAGTGAAAAGTTTCTGA  
ACATGGGTGCACCCCTGGGAGTGGGCCTGGGTCTCGTCTTTGTGTCCTCATTGGGATCTATG  
TTTCTTCCACCTACCACCGTGGCTGGTGCCACTCTTTACTCAGTGGCAATGTACGGTGGATT  
AGTTCTTTTCAGCATGTTCCCTTCTGTATGATACCCAGAAAGTAATCAAGCGTGCAGAAGTAT  
CACCAATGTATGGAGTTCAAAAATATGATCCCATTAACCTCGATGCTGAGTATCTACATGGAT  
ACATTAAATATATTTATGCGAGTTGCAACTATGCTGGCAACTGGAGGCAACAGAAAGAAATG  
AAGTGACTCAGCTTCTGGCTTCTCTGCTACATCAAATATCTTGTTTAAATGGGGCAGATATGC  
ATTAAATAGTTTGTACAAGCAGCTTTCGTTGAAGTTTAGAAGATAAGAAACATGTCATCATA  
TTTAAATGTTCCGGTAATGTGATGCCTCAGGTCTGCCTTTTTTTCTGGAGAATAAATGCAGT  
AATCCTCTCCCAAATAAGCACACACATTTTCAATTCTCATGTTTGAGTGATTTTAAAATGTT  
TTGGTGAATGTGAAAACATAAGTTTGTGTCATGAGAATGTAAGTCTTTTTTCTACTTTAAAA  
TTTAGTAGGTTCACTGAGTAACTAAAATTTAGCAAACCTGTGTTTGCATATTTTTTTTGGAGT  
GCAGAATATTGTAATTAATGTCATAAGTGATTTGGAGCTTTGGTAAAGGGACCAGAGAGAAG  
GAGTCACCTGCAGTCTTTTGTTTTTTTTAAATACTTAGAACTTAGCACTTGTGTTATTGATTA  
GTGAGGAGCCAGTAAGAAACATCTGGGTATTTGGAAACAAGTGGTCATTGTTACATTCATTT  
GCTGAACTTAACAAAACCTGTTTCATCCTGAAACAGGCACAGGTGATGCATTCTCCTGCTGTTG  
CTTCTCAGTGCTCTCTTTCCAATATAGATGTGGTCATGTTTGACTTGTACAGAATGTTAATC  
ATACAGAGAATCCTTGATGGAATTATATATGTGTGTTTTACTTTTGAATGTTACAAAAGGAA  
ATAACTTTAAAACCTATTCTCAAGAGAAAATATTCAAAGCATGAAATATGTTGCTTTTTTCCAG  
AATACAAACAGTATACTCATG

**FIGURE 2**

MLAARLVCLRTLPSRVFHPAFTKASPVVKNSITKNQWLLTPSREYATKTRIGIRRGRTGQEL  
KEAALEPSMEKIFKIDQMGRWVAGGAAVGLGALCYGLGLSNEIGAIEKAVIWPQYVKDRI  
HSTYMYLAGSIGLTALSAIAISRTPVLMNFMMRGSWVTIGVTFAAMVGAGMLVRSIPYDQSP  
GPKHLAWLLHSGVMGAVVAPLTILGGPLLIRAAWYTAGIVGGLSTVAMCAPSEKFLNMGAPL  
GVGLGLVVFVSSLGSMFLPPTTVAGATLYSVAMYGGLVLFSMFLLYDTQKVIKRAEVSPMYGV  
QKYDPINSMLSIYMDTLNIFMRVATMLATGGNRKK

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**FIGURE 3**

GAAGGCTGCCTCGCTGGTCCGAATTCGGTGGCGCCACGTCCGCCCCGTCTCCGCCTTCTGCAT  
CGCGGCTTCGGCGGCTTCCACCTAGACACCTAACAGTCGCGGAGCCGGCCGCGTCGTGAGGG  
GGTCGGCACGGGGAGTCGGGCGGTCTTGTGCATCTTGGCTACCTGTGGGTCTGAAGATGTCGG  
ACATCGGAGACTGGTTCAGGAGCATCCCGGCGATCACGCGCTATTGGTTCGCCGCCACCGTC  
GCCGTGCCCTTGGTCGGCAAACCTCGGCCTCATCAGCCCCGGCCTACCTCTTCCTCTGGCCCCGA  
AGCCTTCCTTTATCGCTTTCAGATTTGGAGGCCAATCACTGCCACCTTTTATTTCCCTGTGG  
GTCCAGGAACCTGGATTTCTTTATTTGGTCAATTTATATTTCTTATATCAGTATTCTACGCGA  
CTTGAAACAGGAGCTTTTGATGGGAGGCCAGCAGACTATTTATTCATGCTCCTCTTTAACTG  
GATTTGCATCGTGATTACTGGCTTAGCAATGGATATGCAGTTGCTGATGATTCTCTGATCA  
TGTCAGTACTTTATGTCTGGGCCCAGCTGAACAGAGACATGATTGTATCATTTTGGTTTGGGA  
ACACGATTTAAGGCCTGCTATTTACCCTGGGTATCCTTGGAATCAACTATATCATCGGAGG  
CTCGGTAATCAATGAGCTTATTGGAAATCTGGTTGGACATCTTTATTTTTTCTTAATGTTCA  
GATACCCAATGGACTTGGGAGGAAGAAATTTTCTATCCACACCTCAGTTTTTGTACCGCTGG  
CTGCCCAGTAGGAGAGGAGGAGTATCAGGATTTGGTGTGCCCCCTGCTAGCATGAGGCGAGC  
TGCTGATCAGAATGGCGGAGGCGGGAGACACAACCTGGGGCCAGGGCTTTCGACTTGGAGACC  
AGTGAAGGGGCGGCCTCGGGCAGCCGCTCCTCTCAAGCCACATTTCTCCAGTGCTGGGTG  
CACTTAACAACCTGCGTTCTGGCTAACACTGTTGGACCTGACCCACACTGAATGTAGTCTTTC  
AGTACGAGACAAAGTTTCTTAAATCCCGAAGAAAAATATAAGTGTTCCACAAGTTTCACGAT  
TCTCATTCAAGTCCTTACTGCTGTGAAGAACAAATACCAACTGTGCAAATTGCAAAACTGAC  
TACATTTTTTGGTGTCTTCTCTTCTCCCCTTTCCGTCTGAATAATGGGTTTTAGCGGGTCTT  
AATCTGCTGGCATTGAGCTGGGGCTGGGTACCAAACCCTTCCCAAAGGACCTTATCTCTT  
TCTTGCACACATGCCTCTCTCCCACTTTTCCCAACCCCCACATTTGCAACTAGAAAAAGTTG  
CCCATAAAATTGCTCTGCCCTTGACAGGTTCTGTTATTTATTGACTTTTGCCAAGGCTGGTC  
ACAACAATCATATTCACGTTATTTTCCCCTTTTGGTGGCAGAACTGTTACCAATAGGGGGAG  
AAGACAGCCACGGATGAAGCGTTTCTCAGCTTTTGGGAATTGCTTCGACTGACATCCGTTGTT  
AACCGTTTGCCACTCTTCAGATATTTTTTATAAAAAAGTACCACTGAGTTCATGAGGGCCA  
CAGATTGGTTATTAATGAGATACGAGGGTTGGTGTGTTTGTCTTCTGAGCTAAGTGA  
TCAAGACTGTAGTGGAGTTGCAGCTAACATGGGTTAGGTTTAAACCATGGGGGATGCACCCC  
TTTGCGTTTCATATGTAGCCCTACTGGCTTTGTGTAGCTGGAGTAGTTGGGTTGCTTTGTGT  
TAGGAGGATCCAGATCATGTTGGCTACAGGGAGATGCTCTCTTTGAGAGGTCCTGGGCATTG  
ATTCCCATTTCAATCTCATTCTGGATATGTGTTTATTGAGTAAAGGAGGAGAGACCCTCATA  
CGCTATTTAAATGTCACCTTTTTTGCCTATCCCCCGTTTTTTGGTTCATGTTTCAATTAATTGT  
GAGGAAGGCGCAGCTCCTCTCTGCACGTAGATCATTTTTTTAAAGCTAATGTAAGCACATCTA  
AGGGAATAACATGATTTAAGGTTGAAATGGCTTTAGAATCATTTGGGTTTGAGGGTGTGTTA  
TTTTGAGTCATGAATGTACAAGCTCTGTGAATCAGACCAGCTTAAATACCCACACCTTTTTT  
TCGTAGGTGGGCTTTTCTATCAGAGCTTGGCTCATAACCAAATAAAGTTTTTTGAAGGCCA  
TGGCTTTTTCACACAGTTATTTTATTTTATGACGTTATCTGAAAGCAGACTGTTAGGAGCAGT  
ATTGAGTGGCTGTCACACTTTGAGGCAACTAAAAAGGCTTCAAACGTTTTTGATCAGTTTCTT  
TTCAGGAAACATTGTGCTCTAACAGTATGACTATTCTTTCCCCCACTCTTAAACAGTGTGAT  
GTGTGTTATCCTAGGAAATGAGAGTTGGCAAACAACCTTCTCATTTTGAATAGAGTTTGTGTG  
TACTTCTCCATATTTAATTTATATGATAAAATAGGTGGGGAGAGTCTGAACCTTAACTGTCA  
TGTTTTTGTGTTTTCATCTGTGGCCACAATAAAGTTTACTTGTAATAATTTTAGAGGCCATTACT  
CCAATTATGTTGCACGTACACTCATTGTACAGGCGTGGAGACTCATTGTATGTATAAGAATA  
TTTCTGACAGTGAGTGACCCGGAGTCTCTGGTGTACCTCTTACCAGTCAGCTGCCTGCGAG  
CAGTCATTTTTTCTTAAAGGTTTACAAGTATTTAGAAGCTTTTCAGTTCAGGGCAAAATGTTT  
ATGAAGTTATTCCTCTTAAACATGGTTAGGAAGCTGATGACGTTATTGATTTTGTCTGGATT  
ATGTTTCTGGAATAATTTTACCAAACAAGCTATTTGAGTTTTGACTTGACAAGGCAAAACA  
TGACAGTGGATTCTCTTTACAAATGGAATAAAATCCTTATTTTGTATAAAGGACTTCCC  
TTTTTGTAACATAATCCTTTTTTATTGGTAAAAATTGTAAATTAATAATGTGCAACTTG

**FIGURE 4**

MSDIGDWFRSIPAITRYWFAATVAVPLVGKLGLISPAYLFLWPEAFLYRFQIWRPITATFYF  
PVGPGTGFLYLVNLYFLYQYSTRLETGAFDGRPADYLFMLLENWICIVITGLAMDMQLLMIP  
LIMSVLYVWAQLNRDMIVSFWEGTRFKACYLPWVILGFNYIIGGSVINELIGNLVGHLYFFL  
MFRYPMDLGGRNFLSTPQFLYRWLPSRRGGVSGFGVPPASMRRAADQNGGGGRHNWGQGFRLGDQ



**FIGURE 5**

GGGGCCGCGGTCTAGGGCGGCTACGTGTGTTGCCATAGCGACCATTTTGCATTA ACTGGTTG  
GTAGCTTCTATCCTGGGGGCTGAGCGACTGCGGGCCAGCTCTTCCCCTACTCCCTCTCGGCT  
CCTTGTGGCCCAAAGGCCTAACCGGGGTCCGGCGGTCTGGCCTAGGGATCTTCCCCGTTGCC  
CCTTTGGGGCGGGATGGCTGCGGAAGAAGAAGACGAGGTGGAGTGGGTAGTGGAGAGCATCG  
CGGGGTTCCCTGCGAGGCCCAGACTGGTCCATCCCCATCTTGGACTTTGTGGAACAGAAATGT  
GAAGTTAACTGCAAAGGAGGGCATGTGATAACTCCAGGAAGCCCAGAGCCGGTGATTTTGGT  
GGCCTGTGTTCCCCTTGTTTTTGTATGATGAAGAAGAAAGCAAATTGACCTATACAGAGATTC  
ATCAGGAATACAAAGAACTAGTTGAAAAGCTGTTAGAAGGTTACCTCAAAGAAATTGGAATT  
AATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGCAAAGACCCATACATCACAGGC  
CATTTTGCAACCTGTGTTGGCAGCAGAAGATTTTACTATCTTTAAAGCAATGATGGTCCAGA  
AAACATTGAAATGCAGCTGCAAGCCATTCGAATAATTCAAGAGAGAAATGGTGTATTACCT  
GACTGCTTAACCGATGGCTCTGATGTGGTCAGTGACCTTGAACACGAAGAGATGAAAATCCT  
GAGGGAAGTTCTTAGAAAATCAAAAGAGGAATATGACCAGGAAGAAGAAAGGAAGAGGAAAA  
AACAGTTATCAGAGGCTAAAACAGAAGAGCCCACAGTGCATTCCAGTGAAGCTGCAATAATG  
AATAATTCCCAAGGGGATGGTGAACATTTTGCACACCCACCCTCAGAAGTTAAATGCATTT  
TGCTAATCAGTCAATAGAACCTTTGGGAAGAAAAGTGGAAAGGTCTGAAACTTCCTCCCTCC  
CACAAAAGGCCTGAAGATTCTTGGCTTAGAGCATGCGAGCATTGAAGGACCAATAGCAAAC  
TTATCAGTACTTGGAACAGAAGAACTTCGGCAACGAGAACACTATCTCAAGCAGAAGAGAGA  
TAAGTTGATGTCCATGAGAAAGGATATGAGGACTAAACAGATACAAAATATGGAGCAGAAAG  
GAAAACCCACTGGGGAGGTAGAGGAAATGACAGAGAAACCAGAAATGACAGCAGAGGAGAAG  
CAAACATTACTAAAGAGGAGATTGCTTGCAGAGAACTCAAAGAAGAAGTTATTAATAAGTA  
ATAATTAAGAACAATTTAACAAAATGGAAGTTCAAATTGTCTTAAAAATAAATTATTTAGTC  
CTTACACTG

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**FIGURE 6**

MAAEEDEVEWVVESIAGFLRGPDWSIPILDFVEQKCEVNCKGGHVITPGSPEPVILVACVP  
LVFDDEEESKLTYTEIHQEYKELVEKLLEGYLKEIGINEDQFQEAactsPLAKTHTSQAILQP  
VLAAEDFTIFKAMMVQKNiEMQLQAIRIIQERNGVLPDCLTDGSDVVSDLEHEEMKILREVL  
RKSKEEYDQEEERKRKKQLSEAKTEEPTVHSSEAAIMNNSQGDGEHFAHPPSEVKMHFANQS  
IEPLGRKVERSETSSLPQKGLKIPGLEHASIEGPiANLSVLGTEELRQREHYLKQKRDKLMS  
MRKDMRTKQIQNMEQKGKPTGEVEEMTEKPEMTAEEKQTLLKRRLLAEKLEEVINK

**FIGURE 7**

GGGCACAGCACATGTGAAGTTTTTGATGATGAAGAAGAAAGCAAATTGACCTATACAGAGAT  
TCATCAGGAATACAAAGAACTAGTTGAAAAGCTGTTAGAAGGTTACCTCAAAGAAATTGGAA  
TTAATGAAGATCAATTTCAAGAAGCATGCACTTCTCCTCTTGCAAAGACCCATACATCACAG  
GCCATTTTTGCAACCTGTGTTGGCAGCAGAAGATTTTACTATCTTTAAAGCAATGATGGTCC  
AGAAAAACATTGAAATGCAGCTGCAAGCCATTGGAATAATTCAAGAGAGAAATGGTGTATTA  
CCTGACTGCTTAACCGATGGCTCTGATGTGGTCAGTGACCTTGAACACGAAGAGATGAAAAT  
CCTGAGGGAAGTTCTTAGAAAATCAAAAGAGGAATATGACCAGGAA

**FIGURE 8**

GCGTGGTTTTTGTCTGCAATAGGCGGCTTAGAGGGAGGGGCTTTTTTCGCCTATACCTACTG  
TAGCTTCTCCACGTATGGACCCTAAAGGCTACTGCTGCTACTACGGGGCTAGACAGTTACTG  
TCTCAGCTCTAGGATGTGCGTTCTTCCACTAGAAGCTCTTCTGAGGGAGGTAATTA AAAAAC  
AGTGGAATGGAAAAACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCAACAATGTATAC  
ATTCCTGCTAGGTGCCATATTCATTGCTTTAAGCTCAAGTCGCATCTTACTAGTGAAGTATT  
CTGCCAATGAAGAAAACAAGTATGATTATCTTCCAACACTACTGTGAATGTGTGCTCAGAACTG  
GTGAAGCTAGTTTTCTGTGTGCTTGTGTCATTCTGTGTTATAAAGAAAGATCATCAAAGTAG  
AAATTTGAAATATGCTTCCTGGAAGGAATTCTCTGATTTTCATGAAGTGGTCCATTCTGCCT  
TTCTTTATTTCTGATAACTTGATTGTCTTCTATGTCCTGTCCTATCTTCAACCAGCCATG  
GCTGTTATCTTCTCAAATTTTAGCATTATAACAACAGCTCTTCTATTCAGGATAGTGCTGAA  
GAGGCGTCTAAACTGGATCCAGTGGGCTTCCCTCCTGACTTTATTTTTGTCTATTGTGGCCT  
TGACTGCCGGGACTAAACTTTACAGCACAACTTGGCAGGACGTGGATTTTCATCACGATGCC  
TTTTTTCAGCCCTTCCAATTCCTGCCTTCTTTTCAGAAGTGAGTGTCCAGAAAAGACAATTG  
TACAGCAAAGGAATGGACTTTTCCTGAAGCTAAATGGAACACCACAGCCAGAGTTTTTCAGTC  
ACATCCGTCTTGGCATGGGCCATGTTCTTATTATAGTCCAGTGTTTTATTTCTTCAATGGCT  
AATATCTATAATGAAAAGATACTGAAGGAGGGGAACCAGCTCACTGAAAGCATCTTCATACA  
GAACAGCAAACCTCTATTTCTTTGGCATTCTGTTTAATGGGCTGACTCTGGGCCTTCAGAGGA  
GTAACCGTGATCAGATTAAGAAGTGTGGATTTTTTTTATGGCCACAGTGCATTTTCAGTAGCC  
CTTATTTTTGTAACTGCATTCCAGGGCCTTTCAGTGGCTTTCATTCTGAAGTTCCTGGATAA  
CATGTTCCATGTCTTGATGGCCCAGGTTACCACTGTCATTATCACAAAGTGTCTGTCCTGG  
TCTTTGACTTCAGGCCCTCCCTGGAATTTTTCTTGGAAGCCCCATCAGTCCTTCTCTCTATA  
TTTATTTATAATGCCAGCAAGCCTCAAGTTCGGAATACGCACCTAGGCAAGAAAGGATCCG  
AGATCTAAGTGGCAATCTTTGGGAGCGTTCCAGTGGGGATGGAGAAGAACTAGAAAGACTTA  
CCAAACCCAAGAGTGATGAGTCAGATGAAGATACTTTCTAACTGGTACCCACATAGTTTGCA  
GCTCTCTTGAACCTTATTTTTCACATTTTTCAGTGTGTTGTAATATTTATCTTTTCACTTTGATA  
AACCAGAAATGTTTCTAAATCCTAATATTCTTTGCATATATCTAGCTACTCCCTAAATGGTT  
CCATCCAAGGCTTAGAGTACCCAAAGGCTAAGAAATTCTAAAGAACTGATACAGGAGTAACA  
ATATGAAGAATTCATTAATATCTCAGTACTTGATAAATCAGAAAGTTATATGTGCAGATTAT  
TTTCCTTGGCCTTCAAGCTTCCAAAAAACTTGTAATAATCATGTTAGCTATAGCTTGTATAT  
ACACATAGAGATCAATTTGCCAAATATTCACAATCATGTAGTTCTAGTTTACATGCCAAAGT  
CTTCCCTTTTTTAACATTATAAAAGCTAGGTTGTCTCTTGAATTTTGAGGCCCTAGAGATAGT  
CATTTTGCAAGTAAAGAGCAACGGGACCCTTTCTAAAAACGTTGGTTGAAGGACCTAAATAC  
CTGGCCATACCATAGATTTGGGATGATGTAGTCTGTGCTAAATATTTTGCTGAAGAAGCAGT  
TTCTCAGACACAACATCTCAGAATTTTAATTTTTTAGAAATTCATGGGAAATTGGATTTTTGT  
AATAATCTTTTGATGTTTTTAACATTGGTTCCCTAGTCACCATAGTTACCACTTGTATTTTA  
AGTCATTTAAACAAGCCACGGTGGGGCTTTTTTCTCCTCAGTTTGAGGAGAAAAATCTTGAT  
GTCATTACTCCTGAATTATTACATTTTGGAGAATAAGAGGGCATTTTATTTTATTAGTTACT  
AATTCAAGCTGTGACTATTGTATATCTTTCCAAGAGTTGAAATGCTGGCTTCAGAATCATAAC  
CAGATTGTCAGTGAAGCTGATGCCTAGGAACCTTTAAAGGGATCCTTTCAAAGGATCACTT  
AGCAAACACATGTTGACTTTTAACTGATGTATGAATATTAATACTCTAAAAATAGAAAGACC  
AGTAATATATAAGTCACTTTACAGTGCTACTTCACACTTAAAGTGCATGGTATTTTTTCATG  
GTATTTTGCATGCAGCCAGTTAACTCTCGTAGATAGAGAAGTCAGGTGATAGATGATATTAA  
AAATTAGCAAACAAAAGTGACTTGCTCAGGGTCATGCAGCTGGGTGATGATAGAAGAGTGGG  
CTTTAACTGGCAGGCCTGTATGTTTACAGACTACCATACTGTAAATATGAGCTTTATGGTGT  
CATTCTCAGAACTTATACATTTCTGCTCTCCTTTCTCCTAAGTTTCATGCAGATGAATATA  
AGGTAATATACTATTATATAATTCATTTGTGATATCCACAATAATATGACTGGCAAGAATTG  
GTGGAAATTTGTAATTAAATAATTATTAAACCT



**FIGURE 9**

MEKQCCSHPVICSLSTMYTFLLGAIFIALSSSRILLVKYSANEENKYDYLPTTVNVCSELVK  
LVFCVLVSFCVIKKDHQSRNLKYASWKEFSDFMKWSIPAFLYFLDNLIVFYVLSYLQPAMAV  
IFS NFSIITTALLFRIVLKRRLNWIQWASLLTLFLSIVALTAGTKTLQHNLAGRGFHHDAFF  
SPSNSCLLFRSECPRKDNCTAKEWTFPEAKWNTTARVFSHIRLGMGHVLIIVQCFISSMANI  
YNEKILKEGNQLTESIFIQNSKLYFFGILFNGLTLGLQRSNRDQIKNCGFFYGHSAFSVALI  
FVTAFQGLSVAFILKFLDNMFHVLMAQVTTVIITTVSVLVFDFRPSLEFFLEAPSVLLSIFI  
YNASKPQVPEYAPRQERIRDLSGNLWERSSSGDGEELERLTKPKSDESEDTF

**FIGURE 10**

CGTGCCTGCGCAATGGGTGTCGGGTCCGCTTTTTCCCAATCCGGACGTAATCGTGGTTTTTG  
TTCTGCAATAGGCGGCTTAGAGGGAGGGGCTTTTTTCGCCTATACCTACTGTAGCTTCTCCAC  
GTATGGACCCTAAAGGCTACTGCTGCTACTACGGGGCTAGACAGTTACTGTCTCAGCTCTAG  
GATGTGCGTTCTTCCACTAGAAGCTCTTCTGAGGGAGGTAATTAAAAAACAGTGGAATGGAA  
AAACAGTGCTGTAGTCATCCTGTAATATGCTCCTTGTCACAATGTATACATTCCTGCTAGG  
TGCCATATTCATTGCTTTAAGCTCAAGTCGCATCTTACTAGTGAAGTATTCTGCCAATGAAG  
AAAACAAGTATGATTATCTTCCAACACTACTGTGAATGTGTGCTCAGAACTGGTGAAGCTAGTT  
TTCTGTGTGCTTGTGTCATTCTGTGTTATAAAGAAAGATCATCAAAGTAGAAATTTGAAATA  
TGCTTCCTGGAAGGAATTCTCTGATTTTCATGAAGTGGTCCATTCCTGCCTTTCTTTATTTCC  
TGGATAACTTGATTGTCTTCTATGTCCTGTCCTATCTTCAACCAGCCATGGCTGTTATCTTC  
TCAAATTTTAGCATTATAACAACAGCTCTTCTATTCAGGATAGTGCTGAAGAGGCGTCTAAA  
CTGGATCCAGTGGGCTTCCCTCCTGACTTTATTTTTGTCTATTGTGGCCTTGACTGCCGGGA  
CTAAAACCTTA

**FIGURE 11**

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGGCCGGCTTGGCTAGCGCGCGGCGGCC  
GTGGCTAAGGCTGCTACGAAGCGAGCTTGGGAGGAGCAGCGGCCTGCGGGGCAGAGGAGCAT  
CCCGTCTACCAGGTCCCAAGCGGCGTGGCCCGCGGGTCATGGCCAAAGGAGAAGGCGCCGAG  
AGCGGCTCCGCGGCGGGGCTGCTACCCACCAGCATCCTCCAAAGCACTGAACGCCCCGGCCCA  
GGTGAAGAAAGAACCGAAAAAGAAGAAACAACAGTTGTCTGTTTGCAACAAGCTTTGCTATG  
CACTTGGGGGAGCCCCCTACCAGGTGACGGGCTGTGCCCTGGGTTTCTTCCTTCAGATCTAC  
CTATTGGATGTGGCTCAGGTGGGCCCTTTCTCTGCCTCCATCATCCTGTTTGTGGGCCGAGC  
CTGGGATGCCATCACAGACCCCCTGGTGGGCCTCTGCATCAGCAAATCCCCCTGGACCTGCC  
TGGGTCGCCTTATGCCCTGGATCATCTTCTCCACGCCCCCTGGCCGTCATTGCCTACTTCCTC  
ATCTGGTTCGTGCCCCGACTTCCCACACGGCCAGACCTATTGGTACCTGCTTTTCTATTGCCT  
CTTTGAAACAATGGTCACGTGTTTCCATGTTCCCTACTCGGCTCTCACCATGTTTCATCAGCA  
ACCGAGCAGACTGAGCGGGATTCTGCCACCGCCTATCGGATGACTGTGGAAGTGCTGGGCAC  
AGTGCTGGGCACGGCGATCCAGGGACAAATCGTGGGCCAAGCAGACACGCCTTGTTTCCAGG  
ACTTCAATAGCTCTACAGTAGCTTCACAAAGTGCCAACCATAACATGGCACCACTTCACAC  
AGGGAAACGCAAAAGGCATACCTGCTGGCAGCGGGGGTCATTGTCTGTATCTATATAATCTG  
TGCTGTCATCCTGATCCTGGGCGTGCGGGAGCAGAGAGAACCCTATGAAGCCCAGCAGTCTG  
AGCCAATCGCCTACTTCCGGGGCCTACGGCTGGTCATGAGCCACGGCCCATAACAACTT  
ATTACTGGCTTCCTCTTCACCTCCTTGGCTTTCATGCTGGTGGAGGGGAACCTTTGTCTTGTT  
TTGCACCTACACCTTGGGCTTCCGCAATGAATTCAGAATCTACTCCTGGCCATCATGCTCT  
CGGCCACTTTAACCATTCCCATCTGGCAGTGGTTCTTGACCCGGTTTGGCAAGAAGACAGCT  
GTATATGTTGGGATCTCATCAGCAGTGCCATTTCTCATCTTGGTGGCCCTCATGGAGAGTAA  
CCTCATCATTACATATGCGGTAGCTGTGGCAGCTGGCATCAGTGTGGCAGCTGCCTTCTTAC  
TACCCTGGTCCATGCTGCCTGATGTCATTGACGACTTCCATCTGAAGCAGCCCCACTTCCAT  
GGAACCGAGCCCATCTTCTTCTCCTTCTATGTCTTCTTCACCAAGTTTGCCTCTGGAGTGTC  
ACTGGGCATTTCTACCCTCAGTCTGGACTTTGCAGGGTACCAGACCCGTGGCTGCTCGCAGC  
CGGAACGTGTCAAGTTTACACTGAACATGCTCGTGACCATGGCTCCCATAGTTCTCATCCTG  
CTGGGCCTGCTGCTCTTCAAAATGTACCCCATTGATGAGGAGAGGGCGGCGGCAGAATAAGAA  
GGCCCTGCAGGCACTGAGGGACGAGGCCAGCAGCTCTGGCTGCTCAGAAACAGACTCCACAG  
AGCTGGCTAGCATCCTCTAGGGGCCCGCCACGTTGCCCCGAAGCCACCATGCAGAAGGCCACAG  
AAGGGATCAGGACCTGTCTGCCGGCTTGCTGAGCAGCTGGACTGCAGGTGCTAGGAAGGGAA  
CTGAAGACTCAAGGAGGTGGCCCAGGACACTTGCTGTGCTCACTGTGGGGCCGGCTGCTCTG  
TGGCCTCCTGCCTCCCCTCTGCCTGCCTGTGGGGCCAAGCCCTGGGGCTGCCACTGTGAATA  
TGCCAAGGACTGATCGGGCCTAGCCCGGAACACTAATGTAGAAACCTTTTTTTTACAGAGCC  
TAATTAATAACTTAATGACTGTGTACATAGCAATGTGTGTGTATGTATATGTCTGTGAGCTA  
TTAATGTTATTAATTTTCATAAAAGCTGGAAAGC

**FIGURE 12**

MWLRWALSLPPSSCLWAEPGMPSQTPWWASASANPPGPAWVALCPGSSSPRPWPSLPTSSSG  
SCPTSHTARPIGTCTFSIASLKQWSRVSMFPTRLSPCSSATEQTERDSATAYRMTVEVLGTVL  
GTAIQGQIVGQADTPCFQDFNSSTVASQSANHTHGTTSHRETQKAYLLAAGVIVCIYIICAV  
ILILGVREQREPYEAAQQSEPIAYFRGLRLVMSHGPIYIKLITGFLFTSLAFMLVEGNFVLFCT  
YTLGFRNEFQNLALLAIMLSATLTIPWQWFLTRFGKKTAVYVGISSAVPFLILVALMESNLI  
ITYAVAVAAGISVAAAFLLPWSMLPDVIDDFHLKQPHFHGTEPIFFSFYVFFTKFASGVSLG  
ISTLSLDFAGYQTRGCSQPERVKFTLNMLVTMAPIVLILLGLLLFKMYPIDEERRRQNKAL  
QALRDEASSSGCSETDSTELASIL



**FIGURE 13**

GGGAAACGCAAAAGGCATACCTGCTGGCAGCGGGGGTCATTGTCTGTATCTATATAATCTGT  
GCTGTCATCCTGATCCTGGGCGTGCGGGAGCAGAGAGAACCCTATGAAGCCCAGCAGTCTGA  
GCCAATCGCCTACTTCCGGGGCCTACGGCTGGTCATGAGCCACGGCCCATACATCAAACCTTA  
TTACTGGCTTCCTCTTCACCTCCTTGGCTTTCATGCTGGTGGAGGGGAACTTTGTCTTGTTT  
TGCACCTACACCTTGGGCTTCCGCAATGAATTCCAGAATCTACTCCTGGCCATCATGCTCTC  
GGCCACTTTAACCATTCCCATCTGGCAGTGGTTCTTGACCCGGTTTGGCAAGAAGACAGCTG  
TATATGTTGGGATCTCATCAGCAGTGCCATTTCTCATCTTGGTGGCCCTCATGGAGAGTAAC  
CTCATCATTACATATGCGGTAGCTGTGGCAGCTGGCATCAGTGTGGCAGCTGCCTTCTTACT  
ACCCTGGTCCATGCTGCCTGATGTCATTGACGACTTCCATCTGAAGCAGCCCCACTTCCATG  
GAACCGAGCCCAT

**FIGURE 14**

GGGGCTTCGGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGGATTTACAAAAGGTGCAGGT  
ATGAGCAGGTCTGAAGACTAACATTTTGTGAAGTTGTAAAACAGAAAACCTGTTAGAAATGT  
GGTGGTTTCAGCAAGGCCTCAGTTTCCTTCCTTCAGCCCTTGTAATTTGGACATCTGCTGCT  
TTCATATTTTCATACATTACTGCAGTAACACTCCACCATATAGACCCGGCTTTACCTTATAT  
CAGTGACACTGGTACAGTAGCTCCAGAAAAATGCTTATTTGGGGCAATGCTAAATATTGCGG  
CAGTTTTATGCATTGCTACCATTTATGTTTCGTTATAAGCAAGTTCATGCTCTGAGTCCTGAA  
GAGAACGTTATCATCAAATTAAACAAGGCTGGCCTTGTAAGTGGAACTGAGTTGTTTAGG  
ACTTTCTATTGTGGCAAACCTTCCAGAAAACAACCCTTTTGTCTGCACATGTAAGTGGAGCTG  
TGCTTACCTTTGGTATGGGCTCATTATATATGTTTGTTCAGACCATCCTTTCCTACCAAATG  
CAGCCCAAATCCATGGCAAACAAGTCTTCTGGATCAGACTGTTGTTGGTTATCTGGTGTGG  
AGTAAGTGCACTTAGCATGCTGACTTGCTCATCAGTTTTGCACAGTGGCAATTTTGGGACTG  
ATTTAGAACAGAACTCCATTGGAACCCCGAGGACAAAGGTTATGTGCTTCACATGATCACT  
ACTGCAGCAGAATGGTCTATGTCATTTTCCTTCTTTGGTTTTTTTCTGACTTACATTCGTGA  
TTTTTCAGAAAATTTCTTTACGGGTGGAAGCCAATTTACATGGATTAACCCTCTATGACACTG  
CACCTTGCCCTATTAACAATGAACGAACACGGCTACTTTCCAGAGATATTTTGATGAAAGGAT  
AAAATATTTCTGTAATGATTATGATTCTCAGGGATTGGGGAAAGGTTACAGAAAGTTGCTTA  
TTCTTCTCTGAAATTTTCAACCACTTAATCAAGGCTGACAGTAACACTGATGAATGCTGATA  
ATCAGGAAACATGAAAGAAGCCATTTGATAGATTATTCTAAAGGATATCATCAAGAAGACTA  
TTAAAAACACCTATGCCTATACTTTTTTTATCTCAGAAAATAAAGTCAAAAGACTATG

**FIGURE 15**

MWWFQQGLSFLPSALVIWTSAAFI FSYITAVTLHHIDPALPYISDTGTVAPEKCLFGAMLNI  
AAVLCIATIIYVRYKQVHALSPEENVIIKLNKAGLVLGILSCLGLSIVANFQKTTLFAAHVSG  
AVLTFGMGSLYMFVQTILSYQMOPKIHGKQVFWIRLLLVIWCGVSALSMLTCSSVLHSGNFG  
TDLEQKLHWNPEDKGYVLHMITTAAEWSMSFSFFGFFLTYYIRDFQKISLRVEANLHGLTLYD  
TAPCPINNERTRLLSRDI

**FIGURE 16**

CGGACGCTTGGGCNGCGCCAGCGGCCAGCGCTAGTCGGTCTGGTAAGTGCCTGATGCCGAGT  
TCCGTCTCTCGGGTCTTTTCCTGGTCCCAGGCAAAGCGGAGCGGAGATCCTCAAACGGCCTA  
GTGCTTCGCGCTTCCGGAGAAAATCAGCGGTCTAATTAATTCCTCTGGTTTGTTGAAGCAGT  
TACCAAGAATCTTCAACCCTTTCCCACAAAAGCTAATTGAGTACACGTTCTGTGAGTACA  
CGTTCCTGTTGATTTACAAAAGGTGCAGGTATGAGCAGGTCTGAAGACTAACATTTTGTGAA  
GTTGTAAACAGAAAACCTGTTAGAAATGTGGTGGTTTCAGCAAGGCCTCAGTTTCCTTCCT  
TCAGCCCTTGTAATTTGGACATCTGCTGCTTTCATATTTTCATACATTACTGCAGTAACACT  
CCACCATATAGACCCGGCTTTACCTTATATCAGTGACACTGGTACAGTANC



**FIGURE 17**

CCCACGCGTCCGCCCCGCGCTGCGTCCCGGAGTGCAAGTGAGCTTCTCGGCTGCCCCGCGGG  
CCGGGGTGCGGAGCCGACATGCGCCCCGCTTCTCGGCCTCCTTCTGGTCTTCGCCGGCTGCAC  
CTTCGCCTTGTACTTGCTGTGACGCGACTGCCCCGCGGGCGGAGACTGGGCTCCACCGAGG  
AGGCTGGAGGCAGGTGCTGTGGTTCCCCTCCGACCTGGCAGAGCTGCGGGAGCTCTCTGAG  
GTCCTTCGAGAGTACCGGAAGGAGCACCAGGCCTACGTGTTCTTGCTCTTCTGCGGCGCCTA  
CCTCTACAAACAGGGCTTTGCCATCCCCGGCTCCAGCTTCCTGAATGTTTTAGCTGGTGCCT  
TGTTTGGGCCATGGCTGGGGCTTCTGCTGTGCTGTGTGTTGACCTCGGTGGGTGCCACATGC  
TGCTACCTGCTCTCCAGTATTTTTGGCAAACAGTTGGTGGTGTCTACTTTCCTGATAAAGT  
GGCCCTGCTGCAGAGAAAGGTGGAGGAGAACAGAAACAGCTTGTTTTTTTTCTTATTGTTTT  
TGAGACTTTTCCCCATGACACCAAACCTGGTTCTTGAACCTCTCGGCCCAATTCTGAACATT  
CCCATCGTGCAGTTCTTCTTCTCAGTTCTTATCGGTTTGATCCCATATAATTCATCTGTGT  
GCAGACAGGGTCCATCCTGTCAACCCTAACCTCTCTGGATGCTCTTTTCTCCTGGGACACTG  
TCTTTAAGCTGTTGGCCATTGCCATGGTGGCATTAATTCCTGGAACCCTCATTAAAAAATTT  
AGTCAGAAACATCTGCAATTGAATGAAACAAGTACTGCTAATCATATACACAGTAGAAAAGA  
CACATGATCTGGATTTTCTGTTTGCCACATCCCTGGACTCAGTTGCTTATTTGTGTAATGGA  
TGTGGTCCTCTAAAGCCCCCTCATTGTTTTTTGATTGCCTTCTATAGGTGATGTGGACACTGTG  
CATCAATGTGCAGTGTCTTTTCAGAAAGGACACTCTGCTCTTGAAGGTGTATTACATCAGGT  
TTTCAAACCAGCCCTGGTGTAGCAGACACTGCAACAGATGCCTCCTAGAAAATGCTGTTTGT  
GGCCGGGCGCGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCCGGTGATTC  
ACAAGGTCAGGAGTTCAAGACCAGCCTGGCCAAGATGGTGAAATCCTGTCTCTAATAAAAAT  
ACAAAAATTAGCCAGGCGTGGTGGCAGGCACCTGTAATCCCAGCTACTCGGGAGGCTGAGGC  
AGGAGAATTGCTTGAACCAAGGTGGCAGAGGTTGCAGTAAGCCAAGATCACACCACTGCACT  
CCAGCCTGGGTGATAGAGTGAGACACTGTCTTGAC

**FIGURE 18**

MRPLLGLLLVFAGCTFALYLLSTR LPRGRR LGSTEEAGGRSLWFPSDLAELREELSEVLREYR  
KEHQAYVFL LFCGAYLYKQGFAIPGSSFLNVLAGALFGPWLGLLLCCVLTSVGATCCYLLSS  
IFGKQLVVSYPDKVALLQRKVEENRNSLFFLLFLRLFPMTPNWFLNLSAPILNIPIVQFF  
FSVLIGLIPYNFICVQTGSILSTLTSLDALFSWDTVFKLLAIAMVALIPGTLIKKFSQKHLQ  
LNETSTANHIHSRKDT

**FIGURE 19**

CCGAGGCGGGAGGAGCCCCGAGGGGGCGCGAGCCCCGCATGAATCATTGTAGTCAATCATTTT  
CCAGTTCTCAGCCGCTCAGTTGTGATCAAGGGACACGTGGTTTCCGAAGTCCAGCTCAGAA  
TAGGAAAATAACTTGGGATTTTATATTGGAAGACATGGATCTTGCTGCCAACGAGATCAGCA  
TTTATGACAACTTTCAGAGACTGTTGATTTGGTGAGACAGACCGGCCATCAGTGTGGCATG  
TCAGAGAAGGCAATTGAAAAATTTATCAGACAGCTGCTGGAAAAGAATGAACCTCAGAGACC  
CCCCCGCAGTATCCTCTCCTTATAGTTGTGTATAAGGTTCTCGCAACCTTGGGATTAATCT  
TGCTCACTGCCTACTTTGTGATTCAACCTTTCAGCCCATTAGCACCTGAGCCAGTGCTTTCT  
GGAGCTCACACCTGGCGCTCACTCATCCATCACATTAGGCTGATGTCCTTGCCCATTGCCAA  
GAAGTACATGTCAGAAAATAAGGGAGTTCCTCTGCATGGGGGTGATGAAGACAGACCCTTTC  
CAGACTTTGACCCCTGGTGGACAAACGACTGTGAGCAGAATGAGTCAGAGCCCATTCTGCC  
AACTGCACTGGCTGTGCCCAGAAACACCTGAAGGTGATGCTCCTGGAAGACGCCCCAAGGAA  
ATTTGAGAGGCTCCATCCACTGGTGATCAAGACGGGAAAGCCCCTGTTGGAGGAAGAGATTC  
AGCATTTTTTGTGCCAGTACCCTGAGGCGACAGAAGGCTTCTCTGAAGGGTTTTTCGCCAAG  
TGGTGGCGCTGCTTTCCTGAGCGGTGGTTCCCATTTCTTATCCATGGAGGAGACCTCTGAA  
CAGATCACAAATGTTACGTGAGCTTTTTCTGTTTTCACTCACCTGCCATTTCCAAAAGATG  
CCTCTTTAAACAAGTGCTCCTTTCTTCACCCAGAACCTGTTGTGGGGAGTAAGATGCATAAG  
ATGCCTGACCTATTTATCATTGGCAGCGGTGAGGCCATGTTGCAGCTCATCCCTCCCTTCCA  
GTGCCGAAGACATTGTCAGTCTGTGGCCATGCCAATAGAGCCAGGGGATATCGGCTATGTGCG  
ACACCACCCACTGGAAGGTCTACGTTATAGCCAGAGGGGTCCAGCCTTTGGTCATCTGCGAT  
GGAACCGCTTTCTCAGAACTGTAGGAAATAGAAGTGTGCACAGGAACAGCTTCCAGAGCCGA  
AAACCAGGTTGAAAGGGGAAAAATAAAAACAAAAACGATGAAACTGCAAAAA

**FIGURE 20**

MDLAANEISIIYDKLSETVDLVRQTGHQCGMSEKAIEKFIRQLLEKNEPQRPPPOYPLLIVVY  
KVLATLGLILLTAYFVIQPFSPLAPEPVLSGAHTWRSLIHHIRLMSLP IAKKYMSENKGVPL  
HGGDEDRPFPDFDPWWTNDCEQNESEPI PANCTGCAQKHLKVMLLEDAPRKFERLHPLVIKT  
GKPLLEEEIQHFLCQYPEATEGFSEGFFAKWWRCFPERWFPPYPWRRPLNRSQMLRELFV  
FTHLPFPKDASLNKCSFLHPEPVVGSKMHKMPDLFIIGSGEAMLQLIPPFQCRRHCSVAMP  
IEPGDIGYVDTTHWKVYVIARGVQPLVICDGTA FSEL



**FIGURE 21**

CCACGGTGTCCGTTCTTCGCCCCGGCGGCAGCTGTCCCCGAGGCGGGAGGAGCCCCGAGGGGCG  
CGAGCCCCGCATGAATCATTGTAGTCAATCATTTTCCAGTTCTCAGCCGTTTCAGTTGTGATC  
AAGGGACACGTGGTTTCCGAACTGCCAGCTCAGAATAGGAAAATAACTTGGGATTTTATATT  
GGAAGACATGGATCTTGCTGCCAACGAGATCAGCATTTATGACAACTTTCAGAGACTGTTG  
ATTTGGTGAGACAGACCGGCCATCAGTGTGGCATGTCAGAGAAGGCAATTGAAAAATTTATC  
AGACAGCTGCTGGAAAAGAATGAACCTCAGAGACCCCCCCCCGCAGTATCCTCTCCTTATAGT  
TGTGTATAAGGTTCTCGCAACCTTGGGATTAATCTTGCTCACTGCCTACTTTGTGATTCAAC  
CTTTCAGCCCATTAGCACCTGAGCCAGTGCTTTGTGGAGCTCAC

**FIGURE 22**

CCCACGCGTCCGCCCACGCGTCCGGCTGAACACCTCTTCTTTGGAGTCAGCCACTGATGAGG  
CAGGGTCCCCACTTGCAGCTGCAGCAGCTGCAGCAGCTGCAGAGCGCTGCTCCTGGCTGGTG  
CCTTGGTGCACGCTGCTAGACCGTGCCCTATGAGCCGCTGGGGCTGCAGTGGGGACTGCC  
CTCCCTGCCACCCACCAATGGCAGCCCCACCTTCTTTGAAGACTTCCAGGCTTTTTGTGCCA  
CACCCGAATGGCGCCACTTCATCGACAAACAGGTACAGCCAACCATGTCCTCCAGTTTCGAAATG  
GACACGTATGCTAAGAGCCACGACCTTATGTCAGGTTTCTGGAATGCCTGCTATGACATGCT  
TATGAGCAGTGGGCAGCGGCGCCAGTGGGAGCGCGCCAGAGTCGTCGGGCCTTCCAGGAGC  
TGGTGCTGGAACCTGCGCAGAGGCGGGCGCGCCTGGAGGGGCTACGCTACACGGCAGTGCTG  
AAGCAGCAGGCAACGCAGCACTCCATGGCCCTGCTGCACTGGGGGGCGCTGTGGCGCCAGCT  
CGCCAGCCCATGTGGGGCCTGGGCGCTGAGGGACACTCCCATCCCCCGCTGGAAACTGTCCA  
GCGCCGAGACATATTCACGCATGCGTCTGAAGCTGGTGCCCAACCATCACTTCGACCCTCAC  
CTGGAAGCCAGCGCTCTCCGAGACAATCTGGGTGAGGTTCCCTGACACCCACCGAGGAGGC  
CTCACTGCCTCTGGCAGTGACCAAAGAGGCCAAAGTGAGCACCCACCCGAGTTGCTGCAGG  
AGGACCAGCTCGGCGAGGACGAGCTGGCTGAGCTGGAGACCCCGATGGAGGCAGCAGAACTG  
GATGAGCAGCGTGAGAAGCTGGTGCTGTCGGCCGAGTGCCAGCTGGTGACGGTAGTGGCCGT  
GGTCCCAGGGCTGCTGGAGGTCACCACACAGAATGTATACTTCTACGATGGCAGCACTGAGC  
GCGTGGAACCGAGGAGGGCATCGGCTATGATTTCCGGCGCCCACTGGCCCAGCTGCGTGAG  
GTCCACCTGCGGCGTTTCAACCTGCGCCGTTTCAGCACTTGAGCTCTTCTTTATCGATCAGGC  
CAACTACTTCCTCAACTTCCCATGCAAGGTGGGCACGACCCAGTCTCATCTCCTAGCCAGA  
CTCCGAGACCCAGCCTGGCCCCATCCCACCCCATACCCAGGTACGGAACCAGGTGTACTCG  
TGGCTCCTGCGCCTACGGCCCCCTCTCAAGGCTACCTAAGCAGCCGCTCCCCCAGGAGAT  
GCTGCGTGCTCAGGCCTTACCCAGAAATGGGTACAGCGTGAGATATCCAATTCGAGTACT  
TGATGCAACTCAACACCATTGCGGGGCGGACCTACAATGACCTGTCTCAGTACCCTGTGTTC  
CCCTGGGTCTGCAAGGACTACGTGTCCCAACCCTGGACCTCAGCAACCAGCCGTCTTCCG  
GGACCTGTCTAAGCCCATCGGTGTGGTGAACCCCAAGCATGCCAGCTCGTGAGGGAGAAGT  
ATGAAAGCTTTGAGGACCCAGCAGGGACCATTGACAAGTTCCACTATGGCACCCACTACTCC  
AATGCAGCAGGCGTGATGCACTACCTCATCCGCGTGAGGCCCTTCACCTCCCTGCACGTCCA  
GCTGCAAAGTGGCCGCTTTGACTGCTCCGACCGGCAGTTCCTCGGTGGCGGCAGCCTGGC  
AGGCACGCTGGAGAGCCCTGCCGATGTGAAGGAGCTCATCCCGGAATTCTTCTACTTTCTT  
GACTTCCTGGAGAACCAGAACGGTTTTGACCTGGGCTGTCTCCAGCTGACCAACGAGAAGGT  
AGGCGATGTGGTGCTACCCCCGTGGGCCAGCTCTCCTGAGGACTTCATCCAGCAGCACCGCC  
AGGCTCTGGAGTCGGAGTATGTGTCTGCACACCTACACGAGTGGATCGACCTCATCTTTGGC  
TACAAGCAGCGGGGGCCAGCCGCCGAGGAGGCCCTCAATGTCTTCTATTACTGCACCTATGA  
GGGGGCTGTAGACCTGGACCATGTGACAGATGAGCGGGAACGGAAGGCTCTGGAGGGCATT  
TCAGCAACTTTGGGCAGACTCCCTGTGAGCTGCTGAAGGAGCCACATCCAATCGGCTCTCA  
GCTGAGGAAGCAGCCCATCGCCTTGACGCTTGACACTAACTCACCTAGCATCTTCCAGCA  
CCTGGACGAACTCAAGGCATTCTTCGCAGAGGTGACTGTGAGTGCCAGTGGGCTGCTGGGCA  
CCCACAGCTGGTTGCCCTATGACCGCAACATAAGCAACTACTTCAGCTTCAGCAAAGACCCC  
ACCATGGGCAGCCACAAGACGCAGCGACTGCTGAGTGGCCCGTGGGTGCCAGGCAGTGGTGT  
GAGTGGACAAGCACTGGCAGTGGCCCCGGATGGAAAGCTGCTATTTCAGCGGTGGCCACTGGG  
ATGGCAGCCTGCGGGTGACTGCACTACCCCGTGGCAAGCTGTTGAGCCAGCTCAGTGCCAC  
CTTGATGTAGTAACCTGCCTTGCACTGGACACCTGTGGCATCTACCTCATCTCAGGCTCCCG  
GGACACCACGTGCATGGTGTGGCGGCTCCTGCATCAGGGTGGTCTGTGAGTAGGCTGGCAC  
CAAAGCCTGTGCAGGTCTGTATGGGCATGGGGCTGCAGTGAGCTGTGTGGCCATCAGCACT  
GAACTTGACATGGCTGTGTCTGGATCTGAGGATGGAAGTGTGATCATAACACTGTACGCCG  
CGGACAGTTTGTAGCGGCACTACGGCCTCTGGGTGCCACATTCCCTGGACCTATTTTCCACC  
TGGCATTGGGGTCCGAAGGCCAGATTGTGGTACAGAGCTCAGCGTGGGAACGTCTGGGGCC  
CAGGTCACCTACTCCTTGACCTGTATTTCAGTCAATGGGAAGTTGCGGGCTTCACTGCCCT  
GGCAGAGCAGCCTACAGCCCTGACGGTGACAGAGGACTTTGTGTTGCTGGGCACCGCCAGT  
GCGCCCTGCACATCCTCCAATAAACACACTGCTCCCGGCCGCGCCTCCCTTGCCCATGAAG  
GTGGCCATCCGCAGCGTGGCCGTGACCAAGGAGCGCAGCCACGTGCTGGTGGGCCTGGAGGA  
TGGCAAGCTCATCGTGGTGGTGCAGGGGAGCCCTCTGAGGTGCGCAGCAGCCAGTTTCGCGC  
GGAAGCTGTGGCGGTCTTCGCGGCGCATCTCCAGGTGTCTCGGGAGAGACGGAATACAAC  
CCTACTGAGGCGCGCTGAACCTGGCCAGTCCGGCTGCTCGGGCCCCCGCCCCGGCAGGCCTG  
GCCCCGGAGGCCCCGCCCAGAAGTCGGCGGGAACACCCCGGGGTGGGCAGCCAGGGGGTGA  
GCGGGGCCACCCCTGCCAGCTCAGGGATTGGCGGGCGATGTTACCCCTCAGGGATTGGCG  
GGCGGAAGTCCCGCCCCCTCGCCGGCTGAGGGGCCGCCCTGAGGGCCAGCACTGGCGTCT

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**FIGURE 23**

MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLEGL  
RYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLKLVPN  
HHFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDELAELETP  
MEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFYDGSTERVETEEGIGYDFRRP  
LAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTPVSSPSQTPRPQPGPIPPHTQV  
RNQVYSWLLRLRPPSQGYLSSRSPQEMLRASGLTQKWVQREISNFEYLMQLNTIAGR TYNDL  
SQYPVFPWVLQDYVSPTLDLSNPAVFRDLSKPIGVVNPKHAQLVREKYESFEDPAGTIDKFH  
YGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFDCSDRQFHSVAAAWQARLESPADV KELIP  
EFFYFPDFLENQNGFDLGCLQLTNEKVGDVVLPPWASSPEDFIQQHRQALESEYVSAHLHEW  
IDLI FG YKQRGPA AEEALNVFY YCTYEGAVDLDHVTDERERKALEGIISNFGQTPCQLLKEP  
HPTRL SAE EAAHRLARLDTNSPSIFQHLDELKAFFAEVTVSASGLLGTHSWLPYDRNISNYF  
SFSKDPTMGSHKTQRLLSGPWVPGSGVSGQALAVAPDGKLLFSGGHWGSLRVTALPRGKLL  
SQLSCHLDVVTCLALDTCGIY LISGSRD TCMVWRL LHQGGLSVGLAPKPVQVLYGHGA AVS  
CVAISTELDMAVSGSEDGTVIIHTVRRGQFVAALRPLGATFPGPIFHLALGSEGQIVVQSSA  
WERPGAQVTYSLHLYSVNGKLRASLPLAEQPTALTVTEDFVLLGTAQCALHILQLNTLLPAA  
PPLPMKVAIRSVAVTKERSHVLVGLEDGKLIVV VAGQPSEVRSSQFARKLWRSSRRISQVSS  
GETEYNPTEAR

**FIGURE 24**

CGGACGCGTGGGCGGACGCGTGGGGGCTGTGAGAAAGTGCCAATAAATACATCATGCAACCC  
CACGGCCCACCTTGTGAACTCCTCGTGCCCAGGGCTGATGTGCGTCTTCCAGGGCTACTCAT  
CCAAAGGCCTAATCCAACGTTCTGTCTTCAATCTGCAAATCTATGGGGTCCTGGGGCTCTTC  
TGGACCCTTAACTGGGTACTGGCCCTGGGCCAATGCGTCCTCGCTGGAGCCTTTGCCTCCTT  
CTACTGGGCCTTCCACAAGCCCCAGGACATCCCTACCTTCCCCTTAATCTCTGCCTTCATCC  
GCACACTCCGTTACCACACTGGGTCATTGGCATTGTTGGAGCCCTCATCCTGACCCTTGTGCAG  
ATAGCCCGGGTCATCTTGGAGTATATTGACCACAAGCTCAGAGGAGTGCAGAACCCTGTAGC  
CCGCTGCATCATGTGCTGTTTCAAGTGCTGCCTCTGGTGTCTGGAAAAATTTATCAAGTTCC  
TAAACCGCAATGCATACATCATGATCGCCATCTACGGGAAGAATTTCTGTGTCTCAGCCAAA  
AATGCGTTCATGCTACTCATGCGAAACATTGTCAGGGTGGTCGTCCTGGACAAAGTCACAGA  
CCTGCTGCTGTTCTTTGGGAAGCTGCTGGTGGTCGGAGGCGTGGGGGTCTGTCCTTCTTTT  
TTTTCTCCGGTCGCATCCCGGGGCTGGGTAAAGACTTTAAGAGCCCCCACCTCAACTATTAC  
TGGCTGCCCATCATGACCTCCATCCTGGGGGCCTATGTCATCGCCAGCGGCTTCTTCAGCGT  
TTTCGGCATGTGTGTGGACACGCTCTTCCTCTGCTTCCTGGAAGACCTGGAGCGGAACAACG  
GCTCCCTGGACCGGCCCTACTACATGTCCAAGAGCCTTCTAAAGATTCTGGGCAAGAAGAAC  
GAGGCGCCCCCGGACAACAAGAAGAGGAAGAAGTGACAGCTCCGGCCCTGATCCAGGACTGC  
ACCCACCCCCACCGTCCAGCCATCCAACCTCACTTCGCCTTACAGGTCTCCATTTTGTGGT  
AAAAAAAGGTTTTAGGCCAGGCGCCGTGGCTCACGCCTGTAATCCAACACTTTGAGAGGCTG  
AGGCGGGCGGATCACCTGAGTCAGGAGTTCGAGACCAGCCTGGCCAACATGGTGAAACCTCC  
GTCTCTATTAAAAATACAAAAATTAGCCGAGAGTGGTGGCATGCACCTGTCATCCCAGCTAC  
TCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCAGAGGTTGCAGTGAGCCGAGA  
TCGCGCCACTGCACTCCAACCTGGGTGACAGACTCTGTCTCCAAAACAAAACAAAACAA  
AAAGATTTTATTAAAGATATTTTGTTAACCTC



**FIGURE 25**

RTRGRTRGGCEKVPINTSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLG  
LFWTLNWLALGQCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGALILTLVQ  
IARVILEYIDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNFCVSAK  
NAFMLLMRNIVRVVLDKVTDLLFFGKLLVGGVGVLSFFFFSGRIPGLGKDFKSPHLNYY  
WLPIMTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSLDRPYYSKSLKILGKKN  
EAPPDNKKRKK

**FIGURE 26**

GAGTCTTGACCGCCGCCGGGCTCTTGGTACCTCAGCGCGAGCGCCAGGCGTCCGGCCGCCGT  
GGCTATGTTCGTGTCCGATTTCCGCAAAGAGTTCTACGAGGTGGTCCAGAGCCAGAGGGTCC  
TTCTCTTCGTGGCCTCGGACGTGGATGCTCTGTGTGCGTGCAAGATCCTTCAGGCCTTGTTTC  
CAGTGTGACCACGTGCAATATACGCTGGTTCCAGTTTCTGGGTGGCAAGAACTTGAAACTGC  
ATTTCTTGAGCATAAAGAACAGTTTCATTATTTTATTCTCATAAACTGTGGAGCTAATGTAG  
ACCTATTGGATATTCTTCAACCTGATGAAGACACTATATTCTTTGTGTGTGACTCCCATAGG  
CCAGTCAATGTCGTCAATGTATACAACGATACCCAGATCAAATTACTCATTAAACAAGATGA  
TGACCTTGAAGTTCCCGCCTATGAAGACATCTTCAGGGATGAAGAGGAGGATGAAGAGCATT  
CAGGAAATGACAGTGATGGGTGAGAGCCTTCTGAGAAGCGCACACGGTTAGAAGAGGAGATA  
GTGGAGCAAACCATGCGGAGGAGGCAGCGGCGAGAGTGGGAGGCCCGGAGAAGAGACATCCT  
CTTTGACTACGAGCAGTATGAATATCATGGGACATCGTCAGCCATGGTGATGTTTGAGCTGG  
CTTGGATGCTGTCCAAGGACCTGAATGACATGCTGTGGTGGGCCATCGTTGGACTAACAGAC  
CAGTGGGTGCAAGACAAGATCACTCAAATGAAATACGTGACTGATGTTGGTGTCTCTGCAGCG  
CCACGTTTCCCGCCACAACCACCGGAACGAGGATGAGGAGAACACACTCTCCGTGGACTGCA  
CACGGATCTCCTTTGAGTATGACCTCCGCCTGGTGCTCTACCAGCACTGGTCCCTCCATGAC  
AGCCTGTGCAACACCAGCTATACCGCAGCCAGGTTCAAGCTGTGGTCTGTGCATGGACAGAA  
GCGGCTCCAGGAGTTCCTTGACAGACATGGGTCTTCCCCTGAAGCAGGTGAAGCAGAAGTTCC  
AGGCCATGGACATCTCCTTGAAGGAGAATTTGCGGGAAATGATTGAAGAGTCTGCAAATAAA  
TTTGGGATGAAGGACATGCGCGTGCAGACTTTCAGCATTCATTTTGGGTTCAGCACAAAGTT  
TCTGGCCAGCGACGTGGTCTTTGCCACCATGTCTTTGATGGAGAGCCCCGAGAAGGATGGCT  
CAGGGACAGATCACTTCATCCAGGCTCTGGACAGCCTCTCCAGGAGTAACCTGGACAAGCTG  
TACCATGGCCTGGAACTCGCCAAGAAGCAGCTGCGAGCCACCCAGCAGACCATTGCCAGCTGC  
CTTTGCACCAACCTCGTCATCTCCAGGGGCCTTTCCTGTACTGCTCTCTCATGGAGGGCAC  
TCCAGATGTCATGCTGTTCTCTAGGCCGGCATCCCTAAGCCTGCTCAGCAAACACCTGCTCA  
AGTCCTTTGTGTGTTTCGACAAAGAACCGGCGCTGCAAACCTGCTGCCCCCTGGTGATGGCTGCC  
CCCCTGAGCATGGAGCATGGCACAGTGACCGTGGTGGGCATCCCCCAGAGACCGACAGCTC  
GGACAGGAAGAACTTTTTTGGGAGGGCGTTTGAGAAGGCAGCGGAAAGCACCAGCTCCCGGA  
TGCTGCACAACCATTTTGACCTCTCAGTAATTGAGCTGAAAGCTGAGGATCGGAGCAAGTTT  
CTGGACGCACTTATTTCCCTCCTGTCCTAGGAATTTGATTCTTCCAGAATGACCTTCTTATT  
TATGTAACCTGGCTTTCATTTAGATTGTAAGTTATGGACATGATTTGAGATGTAGAAGCCATT  
TTTTATTAAATAAAATGCTTATTTTAGGAAA

**FIGURE 27**

MFVSDFRKEFYEVVQSQRVLLFVASDVDALCACKILQALFQCDHVQYTLVPVSGWQELETAF  
LEHKEQFHYFILINCGANVDLLDILQPDEDITFFVCDSHRPVNVNVYNDTQIKLLIKQDDD  
LEVPAIEDIFRDEEEDEEHSGNDSGSEPSEKRTRLEEEIVEQTMRRRQRREWEARRRDILF  
DYEQYEHGTSSAMVMFELAWMLSKDLNDMLWWAIVGLTDQWVQDKITQMKYVTDVGVLRH  
VSRHNRNEDEENTLSVDCTRISFEYDLRLVLYQHWSLHDSL CNTSYTAARFKLWSVHGQKR  
LQEF LADMGLPLKQVKQKFQAMD ISLKENLREMIEESANKFGMKDMRVQTF SIHFGFKHKFL  
ASDVVFATMSLMESPEKDGSGTDHFIQALDSLRSNLDKLYHGLELAKKQLRATQQTIASCL  
CTNLVISQGPFLYCSLMEGTPDVMLFSRPASLSLLSKHLLKSFVCSTKNRRCKLLPLVMAAP  
LSMEHGTVTVVGIPPETDSSDRKNFFGRAFEKAAESTSSRMLHNHFDLSVIELKAEDRSKFL  
DALISLLS

**FIGURE 28**

GTACCTCAGCGCGAGCGCCAGGCGTCCGGCCGCGGTGGCTATGNTCGTGTCCGATTTCCGCA  
AAGAGTTCTACGAGGTGGTCCAGAGCCAGAGGGTCCTTCTCTTCGTGGCCTCGGANGTGGAT  
GCTCTGTGTGCGTGCAAGATCCTTCAGGCCTTGTTCCAGTGTGACCANGTGCAATATANGCT  
GGTTCAGTTTCTGGGTGGCAAGAACTTGAAACTGCATTTCTTGAGCATAAAGAACAGTTTC  
ATTATTTTATTCTCATAAACTGTGGAGCTAATGTAGACCTATTGGATATTCTTCAACCTGAT  
GAAGACACTATATTCTTTGTGTGTGACACCCATAGGCCAGTCAATGTTGTCAATGTATACAA  
CGATACCC



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**FIGURE 29**

CAGGAACCCTCTCTTTGGGTCTGGATTGGGACCCCTTTCCAGTACCATTTTTTCTAGTGAAC  
CACGAAGGGACGATACCAGAAAACACCCTCAACCCAAAGGAAATAGACTACAGCCCCAATTG  
GCTGACTTTGGCTATAGAAAAAGAAAGGAACGAAAAGAGACAGTTTTTTTTTGGAAAGCTAA  
GTCTTCCCTTTATCGAGTCAAGAAACCCCCCTTCTTGAGCTATTACAGCTTTTAACAATT  
GAGTAAAGTACGCTCCGGTCACCATGGTGACAGCCGCCCTGGGTCCCGTCTGGGCAGCGCTC  
CTGCTCTTTCTCCTGATGTGTGAGATCCGTATGGTGGAGCTCACCTTTGACAGAGCTGTGGC  
CAGCGGCTGCCAACGGTGCTGTGACTCTGAGGACCCCTGGATCCTGCCCATGTATCCTCAG  
CCTCTTCCTCCGGCCGCCCCACGCCCTGCCTGAGATCAGACCCTACATTAATATCACCATC  
CTGAAGGGTGACAAAGGGGACCCAGGCCCAATGGGCCTGCCAGGGTACATGGGCAGGGAGGG  
TCCCCAAGGGGAGCCTGGCCCTCAGGGCAGCAAGGGTGACAAGGGGGAGATGGGCAGCCCCG  
GCGCCCCGTGCCAGAAGCGCTTCTTCGCCTTCTCAGTGGGCCGCAAGACGGCCCTGCACAGC  
GGCGAGGACTTCCAGACGCTGCTCTTCGAAAGGGTCTTTGTGAACCTTGATGGGTGCTTTGA  
CATGGCGACCGGCCAGTTTGCTGCTCCCCTGCGTGGCATCTACTTCTTCAGCCTCAATGTGC  
ACAGCTGGAATTACAAGGAGACGTACGTGCACATTATGCATAACCAGAAAGAGGCTGTCATC  
CTGTACGCGCAGCCCAGCGAGCGCAGCATCATGCAGAGCCAGAGTGTGATGCTGGACCTGGC  
CTACGGGGACCGCGTCTGGGTGCGGCTCTTCAAGCGCCAGCGCGAGAACGCCATCTACAGCA  
ACGACTTCGACACCTACATCACCTTCAGCGGCCACCTCATCAAGGCCGAGGACGACTGAGGG  
CCTCTGGGCCACCCTCCCGGCTGGAGAGCTCAGGTGCTGGTCCCGTCCCCTGCAGGGCTCAG  
TTTGCACCTGCTGTGAAGCAGGAAGGCCAGGGAGGTCCCCGGGGACCTGGCATTTCTGGGGAGA  
CCCTGCTTCTATCTTGGCTGCCATCATCCCTCCCAGCCTATTTCTGCTCCTCTCTTCTCTCT  
TGGACCTATTTTAAGAAGCTTGCTAACCTAAATATTCTAGAACTTTCCCAGCCTCGTAGCCC  
AGCACTTCTCAAACCTTGGAATGCATGCGAATCACCCGGGGTTCGTGTTAAATGCAGATTCT  
GACTCAGCAGGTCTGAGTGGGTCCAGGATTCTGTGTTTCTCATATGTTCCCTGGGTGATGCTG  
ATGGGGTCAGTCTATGAACCACACTGGAGCAACCAGGTTCTAGGACTTTCTCAATATTCTAG  
TACTTTCTGAACATTCTGGAATCCTCCCCACATTCTAGAATTCTCCCAACATTTTTTTTTTCT  
TGAGACAGAGTCTTGCTCTGTTGCCCAGGCTAGAGTGCAGTGGTGCAATCTCAGTTCACTGC  
AACCTCTGCCTCCCGGGTTCAAGCGATTCTTCTGCCTCAGCCTCCCTAGTGGCTGGGATTAC  
AGGCGCCTGCTACCATGCCTGGCTAATTTTTGTATTTTTTAGTAGAGATGGGGTTTCACCATA  
TTGGCCAGGCTGGTCTTGAACCTCCTGACTTCAGGTGACCCACCCGCCTCGGCCTCTCAAAT  
GCTGGGATTACAGGTGTGAGCCACCGTGCCCTGGCCAATTCCAACATTCTTAAATTCTCTCAT  
CCCTCCAGGGCTCCCCGTGCTATGTTCTCTTTACCCCTTCCCCCTCTTCTCTTGCTCAGGCC  
TGCACCACTGCAGCCACCGTTCATTTATTCAATTCATTAAACACTGAGCACTCACTCTGTGCT  
GGGTCCCGGGAAGGGTGAGGGGGTCAACACAGGCCCTGCCCCTGCCCTCAGTGACTGGCCA  
GTCCAGCCCAGGCGGGGAGAGATGTGTACATAGGTTTTAAAGCAGACCCAGAGCTCATGGGG  
GCCTGTGTTCTGGGTGTTTCAGGTGCTGCTGGTCCCTCCATTACCCACTGCTCCCCAAGGCTGG  
TGGGACGGGGTCCCGGTGGCAGGGGCAGGTATCTCCTTCCCGTTCCTCATCCACCTGCCAG  
TGCTCATCGTTACAGCAAACCCAGGGGGCCTTGGCCAGGTCAAGGGTTCTGTGAGGAGAGG  
ACCCAGGAGTGTGGGGGCATTTGGGGGGTGAAGTGGCCCCCGAAGAATGGAACCCACACCCA  
TAGCTCTCCCCACAGCTGATACGGCATCCTGCGAGAAGACCTGCCCTCCTCACTGGGATCCC  
CTTCCTGCCTCCTCCCAGGGCTCTGCCAGGGCCTTGCTCAGTCCCTTCCACCAAAGTCATCT  
GAACTTCCGTTTCCCCAGGGCCTCCAGCTGCCCTCAGACACTGATGTCTGTCCCCAGGTGCT  
CTCTGCCCCCTCATGCCCCCTCTACCGGCCCAGTGCCCCGACTCTCCAGGCTTTATCAAGGTG  
CTAAGGCCCGGGTGGGCAGCTCCTCGTCTCAGAGCCCTCCTCCGGCCTGGTGCTGCCTTTAC  
AAACACCTGCAGGAGAAGGGCCACGGAAGCCCCAGGCTTTAGAGCCCTCAGCAGGTCTGGGG  
AGCTAGAGCAAAGGAGGGACCTCAGGCCTTCCGTTTCTTCTTCCAGGGTGGGGTGGCCTGGT  
GTTCCCTAGCCTTCCAAACCCAGGTGGCCTGCCCTTCTCCCCAGAGGGAGGCGGCCTCCGC  
CCATTGGTGCTCATGCAGACTCTGGGGCTGAGGTGCCCCGGGGGGTGTCTCTGGTGCTCAC  
AGCCGAGGGAGCCGTGGCTCCATGGCCAGATGACGGAAACAGGGTCTGACCAAGTGCCAGGA  
AGACCTGTGCTATAAACCACCCTGCCTGATCCTGCCCCCTGCCTGACCCCGCCACGCCCTGCC  
GTCCAGCATGATTAAAGAATGCTGTCTCCTCTTGGAATAAAAAAAAAAAAAA

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**FIGURE 30**

MVTAALGPVWAALLLFLLMCEIRMVELTFDRAVASGCQRCCDSEDPLDPAHVSSASSSGRPH  
ALPEIRPYINITILKGDKGDPGPMGLPGYMGREGPGQGEPPQGSKGDKGEMGSPGAPCQKRF  
FAFSVGRKTALHSGEDFQTLLFERVFNLDGCFDMATGQFAAPLRGIYFFSLNVHSWNYKET  
YVHIMHNQKEAVILYAQPSESRIMQSQSVMLDLAYGDRVWVRLFKRQRENAIYSNDFDTYIT  
FSGHLIKAEDD

**Important features:**

**Signal peptide:**

amino acids 1-20

**N-glycosylation site.**

amino acids 72-75

**Clq domain proteins.**

amino acids 144-178, 78-111 and 84-117

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**FIGURE 31**

ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCCTCGGGCCCGACCCGCCAGGAAAGACTG  
AGGCCGCGGCCTGCCCCGCCCCGGCTCCCTGCGCCGCGCGCCCTCCCGGGACAGAAGATGTG  
CTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGGTGCAAGG  
GCTGCCCCATCCGGCTGCCAGTGCAGCCAGCCACAGACAGTCTTCTGCACTGCCCGCCAGGGG  
ACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGGGGCTGTACGTCTTTGAGAACGGCAT  
CACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCCTGGACCTGTCAC  
AGAACCAGATCGCCAGCCTGCCAGCGGGGTCTTCCAGCCACTCGCCAACCTCAGCAACCTG  
GACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCCGTGGCCTGCGGCGCCT  
CGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGCCTGGTGCTTCGACACGC  
TCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGCGGGCACTGCCCCCGCTGCGC  
CTGCCCCGCCTGCTGCTGCTGGACCTCAGCCACAACAGCCTCCTGGCCCTGGAGCCCGGCAT  
CCTGGACACTGCCAACGTGGAGGCGCTGCGGCTGGCTGGTCTGGGGCTGCAGCAGCTGGACG  
AGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACCTGGATGTGTCCGACAACAGCTGGAG  
CGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCCTGACGCGCCTGCGGCTGGCCGGCAACAC  
CCGCATTGCCCAGCTGCGGCCCGAGGACCTGGCCGGCCTGGCTGCCCTGCAGGAGCTGGATG  
TGAGCAACCTAAGCCTGCAGGCCCTGCCTGGCGACCTCTCGGGCCTCTTCCCCCGCCTGCGG  
CTGCTGGCAGCTGCCCGCAACCCCTTCAACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCTG  
GGTGCGCGAGAGCCACGTCACACTGGCCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCA  
AGAACGCTGGCCGGCTGCTCCTGGAGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACC  
ACCACAGCCACAGTGCCCAACCACGAGGCCCGTGGTGCGGGAGCCCAACAGCCTTGTCTTCTAG  
CTTGGCTCCTACCTGGCTTAGCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCA  
CTGCCCCACCGACTGTAGGGCCTGTCCCCCAGCCCCAGGACTGCCACCGTCCACCTGCCTC  
AATGGGGGCACATGCCACCTGGGGACACGGCACCACCTGGCGTGCTTGTGCCCCGAAGGCTT  
CACGGGCCTGTACTGTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCA  
CGCCGAGGCCACCACGGTCCCTGACCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGC  
GTGGGGCTGCAGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTA  
TCGCAACCTATCGGGCCCTGATAAGCGGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTG  
AGTACACGGTCACCCAGCTGCGGCCCAACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGG  
CCCGGGCGGGTGCCGGAGGGCGAGGAGGCCTGCGGGGAGGCCCATACACCCCAAGCCGTCCA  
CTCCAACCACGCCCCAGTCACCCAGGCCCGCGAGGGCAACCTGCCGCTCCTCATTTGCGCCCG  
CCCTGGCCGCGGTGCTCCTGGCCGCGCTGGCTGCGGTGGGGGCAGCCTACTGTGTGCGGCGG  
GGGCGGGCCATGGCAGCAGCGGCTCAGGACAAAGGGCAGGTGGGGCCAGGGGCTGGGCCCCCT  
GGAACCTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCGAAGGCAACAGAGGGCGGTGGAG  
AGGCCCTGCCAGCGGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCCAGGGCCTGGCCTC  
CAGTCACCCCTCCACGCAAAGCCCTACATCTAAGCCAGAGAGAGACAGGGCAGCTGGGGCCG  
GGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTGCTGCCACACCACGTAAGTTCTCAGTCC  
CAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGACCACAGCTGGGCCCTGTTCCCTCTGGA  
CCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCCCTAACGTCCCCAGAAC  
CGAGTGCTTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTGCAGTCCCTGGGCACGGCG  
GGCCCTGCCATGTGCTGGTAACGCATGCCTGGGTCTGCTGGGCTCTCCCACTCCAGGCGGA  
CCCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAGGGAGAGCGGGTAGGCGGCTGTG  
TGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAAGAACTGGAAAGGAAGATGCTTTA  
GGAACATGTTTTTGCTTTTTTAAATATATATATTTATAAGAGATCCTTTCCCATTTATTCTG  
GGAAGATGTTTTTCAAACCTCAGAGACAAGGACTTTGGTTTTTTGTAAGACAAACGATGATATG  
AAGGCCTTTTGTAAGAAAAAATAAAAGATGAAGTGTGAAA

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**FIGURE 32**

MCSRVP LLLPL LLLL LALGPGVQGCPSGCQCSQPQTVFCTARQGT TVPRDVPPDTVGLYVFEN  
GITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETFRGLR  
RLERLYLGKNRIRHIQPGAFDTLDRLLLELKLQDNELRALPPLRLPRL LLLDL SHNSLLALEP  
GILDTANVEALRLAGLGLQQLDEGLFSRLRNLDLDVSDNQLERVPPVIRGLRGLTRLRLAG  
NTRIAQLRPEDLAGLAALQELDVSNSLQALPGDLSGLFPRLRLLAAARNPFNCVCPLSWFG  
PWVRESHVTLASPEETRCHFP PKNAGRLLLELDYADFGCPATTTTATVPTTRPVVREPTALS  
SSLAPTWLSPTAPATEAPSPSTAPPTVGPVPQPQDCPPSTCLNGGTCHLGTRHHLACLCPE  
GFTGLYCESQMGQGTRPSPTPVTPRP PPSLT LGIEPVSPTSLRVGLQRYLQGSSVQLRSLRL  
TYRNLSGPDKRLVTLRLPASLAEYTVTQLRP NATYSVCVMPLGPGRVPEGEEACGEAHTPPA  
VHSNHAPVTQAREGNLPLLIAPALAAVLLAALAAVGAAYCVRRGRAMAAAAQDKGQVGPAG  
PLELEGVKVPLEPGPKATEGGGEALPSGSECEVPLMGFP GPGLQSPLHAKPYI



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**FIGURE 33**

GAATCATCCACGCACCTGCAGCTCTGCTGAGAGAGTGCAAGCCGTGGGGGTTTTGAGCTCAT  
CTTCATCATTCATATGAGGAAATAAGTGGTAAATCCTTGGAAATACAATGAGACTCATCAG  
AAACATTTACATATTTTGTAGTATTGTTATGACAGCAGAGGGTGATGCTCCAGAGCTGCCAG  
AAGAAAGGGAAGTATGACCAACTGCTCCAACATGTCTCTAAGAAAGGTTCCCGCAGACTTG  
ACCCAGCCACAACGACACTGGATTTATCCTATAACCTCCTTTTTTCAACTCCAGAGTTCAGA  
TTTTCATTTCTGTCTCCAAACTGAGAGTTTTGATTCTATGCCATAACAGAATTCAACAGCTGG  
ATCTCAAAACCTTTGAATTCAACAAGGAGTTAAGATATTTAGATTTGTCTAATAACAGACTG  
AAGAGTGTAAGTTGGTATTTACTGGCAGGTCTCAGGTATTTAGATCTTTCTTTTAATGACTT  
TGACACCATGCTTATCTGTGAGGAAGCTGGCAACATGTCACACCTGGAAATCCTAGGTTTGA  
GTGGGGCAAAAATACAAAATCAGATTTCCAGAAAATTGCTCATCTGCATCTAAATACTGTC  
TTCTTAGGATTCAGAACTCTTCCTCATTATGAAGAAGGTAGCCTGCCCATCTTAAACACAAC  
AAAAGTGCACATTGTTTTACCAATGGACACAAATTTCTGGGTCTTTTGGCGTGATGGAATCA  
AGACTTCAAAAATATTAGAAATGACAAATATAGATGGCAAAAGCCAATTTGTAAGTTATGAA  
ATGCAACGAAATCTTAGTTTAGAAAATGCTAAGACATCGGTCTATTGCTTAATAAAGTTGA  
TTTACTCTGGGACGACCTTTTCTTATCTTACAATTTGTTTGGCATAACATCAGTGGAACT  
TTCAGATCCGAAATGTGACTTTTGGTGGTAAGGCTTATCTTGACCACAATTCATTTGACTAC  
TCAAATACTGTAATGAGAACTATAAAATTGGAGCATGTACATTTAGAGTGTTTTACATTCA  
ACAGGATAAAATCTATTTGCTTTTGACCAAAATGGACATAGAAAACCTGACAATATCAAATG  
CACAAATGCCACACATGCTTTTCCCGAATTATCCTACGAAATTCGAATATTTAAATTTTGGC  
AATAATATCTTAACAGACGAGTTGTTTAAAGAAGTATCCAAGTGCCTCACTTGAAAAGTCT  
CATTTTGAATGGCAATAAACTGGAGACACTTTCTTTAGTAAGTTGCTTTGCTAACAACACAC  
CCTTGGAACTTGGATCTGAGTCAAAATCTATTACAACATAAAAATGATGAAAATTGCTCA  
TGGCCAGAACTGTGGTCAATATGAATCTGTCTATACAATAAATTGTCTGATTCTGTCTTCAG  
GTGCTTGCCCAAAAGTATTCAAATACTTGACCTAAATAATAACCAATCCAACTGTACCTA  
AAGAGACTATTCATCTGATGGCCTTACGAGAACTAAATATTGCATTTAATTTTCTAACTGAT  
CTCCCTGGATGCAGTCATTTAGTAGACTTTAGTTCTGAACATTGAAATGAAGTTTCTCT  
CAGCCCATCTCTGGATTTTGTTCAGAGCTGCCAGGAAGTTAAAGTCTAAATGCGGGAAGAA  
ATCCATTCCGGTGTACCTGTGAATTAAGAAATTTTCTATTAGCTTGAAACATATTCAGAGGTC  
ATGATGGTTGGATGGTCAGATTCATACACCTGTGAATACCCTTTAAACCTAAGGGGAAGT  
GTTAAAGACGTTTCATCTCCACGAATTATCTTGCAACACAGCTCTGTTGATTGTCACCATG  
TGGTTATTATGCTAGTTCTGGGGTTGGCTGTGGCCTTCTGCTGTCTCCACTTTGATCTGCCC  
TGGTATCTCAGGATGCTAGGTCAATGCACACAAACATGGCACAGGGTTAGGAAAACAACCA  
AGAACAACCTCAAGAGAAATGTCCGATTCCACGCATTTATTTTATACAGTGAACATGATTCTC  
TGTGGGTGAAGAATGAATTGATCCCCAATCTAGAGAAGGAAGATGGTTCTATCTTGATTGTC  
CTTTATGAAAGCTACTTTGACCTGGCAAAAGCATTAGTGAAAATATTGTAAGCTTCATTGA  
GAAAAGCTATAAGTCCATCTTTGTTTTGTCTCCCAACTTTGTCCAGAATGAGTGGTGCCATT  
ATGAATTCTACTTTGCCACCACAATCTCTTCCATGAAAATTCTGATCATATAATTCTTATC  
TTACTGGAACCCATTCCATTCTATTGCATTCCCACCAGGTATCATAAACTGAAAGCTCTCCT  
GGAAAAAAAGCATACTTGAATGGCCCAAGGATAGGCGTAAATGTGGGCTTTTCTGGGCAA  
ACCTTCGAGCTGCTATTAATGTTAATGTATTAGCCACCAGAGAAATGTATGAAGTGCAGACA  
TTCACAGAGTTAAATGAAGAGTCTCGAGGTTCTACAATCTCTCTGATGAGAACAGATTGTCT  
ATAAAATCCCACAGTCCTTGGGAAGTTGGGGACCACATACACTGTTGGGATGTACATTGATA  
CAACCTTTATGATGGCAATTTGACAATATTTATTAAATAAAAAATGGTTATTCCCTTCATA  
TCAGTTTCTAGAAGGATTTCTAAGAATGTATCCTATAGAAACACCTTCACAAGTTTATAAGG  
GCTTATGGAAAAGGTGTTTCATCCCAGGATTGTTTATAATCATGAAAATGTGGCCAGGTGC  
AGTGGCTCACTCTTGTAATCCCAGCACTATGGGAGGCCAAGGTGGGTGACCCACGAGGTCAA  
GAGATGGAGACCATCCTGGCCAACATGGTGAAACCTGTCTCTACTAAAAATACAAAAATTA  
GCTGGGCGTGATGGTGCACGCCTGTAGTCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATCG  
CTTGAACCCGGGAGGTGGCAGTTGCAGTGAGCTGAGATCGAGCCACTGCACTCCAGCCTGGT  
GACAGAGCGAGACTCCATCTCAAAAAAAGAAAAAAGAAAAAATGGAAAACATCC  
TCATGGCCACAAAATAAGGTCTAATTCAATAAATTATAGTACATTAATGTAATATAATATTA  
CATGCCACTAAAAAGAATAAGGTAGCTGTATATTTCTGGTATGGAAAAACATATTAATAT  
GTTATAAACTATTAGGTTGGTGCAAACTAATTGTGGTTTTTGGCCATTGAAATGGCATTGAA  
ATAAAAGTGTAAGAAATCTATACCAGATGTAGTAACAGTGGTTTTGGGTCTGGGAGGTTGGA  
TTACAGGGAGCATTTGATTTCTATGTTGTGTATTTCTATAATGTTTGAATTGTTTAGAATGA  
ATCTGTATTTCTTTTATAAGTAGAAAAAATAAAGATAGTTTTTACAGCCT

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**FIGURE 34**

MRLIRNIYIFCSIVMTAEGDAPELPEERELMTNCSNMSLRKVPADLTPATTTLDLSYNLLFQ  
LQSSDFHSVSKLRVLILCHNRIQQDLKTFEFNKELRYLDLSNNRLKSVTWYLLAGLRYLDL  
SFNDFDTMPICEEAGNMSHLEILGLSGAKIQKSDFQKIAHLHLNTVFLGFRTLPHYEEGSLP  
ILNTTKLHIVLPMDTNFWVLLRDGIKTSKILEMTNIDGKSQFVSYEMQRNLSLENAKTSVLL  
LNKVDLLWDDLFLILQFVWHTSVEHFQIRNVTFGGKAYLDHNSFDYSNTVMRTIKLEHVHFR  
VFYIQQDKIYLLLTkMDIENLTISNAQMPHMLFPNYPTKFQYLNfANNILTDELfKRTIQLP  
HLKTLILNGNKLETLSLVSCFANNTPLEHLDLSONLLQHKNdENCsWPETVVNMNLSYNKLS  
DSVFRCLPKSIQILDlnnnQIQTVPKETIHLMAReLNIAFNfLTDLPgCSHFsrLSVLNIE  
MNFILSPSLDFVQSCQEVKTLNAGRNPFRCTCELKNFIQLETYSEVMMVGWSDSYTCEYPLN  
LRGTRLKDVHLHELSCNTALLIVTIVVIMLVGLAVAFcCLHFDLPWYLRMLGQCTQTWHRV  
RKTTQEQLKRNVRFHAFISYSEHDSLWVKNELIPNLEKEDGSILICLYESYFDPGKSISENI  
VSFIEKSYKSIFVLSPNFVQNEWCHYEFYFAHhNLFHENSdHIILILLEPIPFYCIPTRYHK  
LKALLEKKAYLEWPKDRRKCGLFWANLRAAINVNVLATREMYELQTFTELNEESRGSTISLM  
RTDCL

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**FIGURE 35A**

GGGGGCTTTCTTGGGCTTGGCTGCTTGGAACACCTGCCTCCAAGGACCGGCCTCGGAGGGGT  
CGCCGGGAAAGGGAGGGAAGAAGGAAGGGCGGGGCGGGCCCCCTGCGCCCCGCCCCGCGCCT  
CTGCGCGCCCCCTGTCCGCCCCGGCCCAGCCCAGCCCAGCCCCGCGGGCCGGTCACACGCGCA  
GCCAGCCGGCCGCCTCCCGCGCCCCAAGCGCGCCGCTCTGCTGTGCCCTGCGCCCTTGCCCCG  
CGCCAGCTTCTGCGCCCCGAGCCCGCCCCGGCGCCCCCGGTGACCGTGACCCTGCCCTGGGCG  
CGGGGCGGAGCAGGCATGTCCCGCCCCGGGGACCGCTACCCCAGCGCTGGCCCTGGTGCTCCT  
GGCAGTGACCCTGGCCGGGGTTCGGAGCCCAGGGCGCAGCCCTCGAGGACCCTGATTATTACG  
GGCAGGAGATCTGGAGCCGGGAGCCCTACTACGCGCGCCCCGGAGCCCGAGCTCGAGACCTTC  
TCTCCGCCGCTGCCTGCGGGGCCCCGGGGAGGAGTGGGAGCGGCGCCCCGAGGAGCCCAGGCC  
GCCCAAGAGGGGCCACCAAGCCCCAAGAAAGCTCCCAAGAGGGAGAAGTCGGCTCCGGAGCCGC  
CTCCACCAGGTAAACACAGCAACAAAAAGTTATGAGAACCAAGAGCTCTGAGAAGGCTGCC  
AACGATGATCACAGTGTCCGTGTGGCCCCGTGAAGATGTCAGAGAGAGTTGCCACCTCTTGG  
TCTGGAAACCTTAAAAATCACAGACTTCCAGCTCCATGCCTCCACGGTGAAGCGCTATGGCC  
TGGGGGCACATCGAGGGAGACTCAACATCCAGGCGGGCATTAAATGAAAATGATTTTTTATGAC  
GGAGCGTGGTGCGCGGGAAGAAATGACCTCCAGCAGTGGATTGAAGTGGATGCTCGGCGCCT  
GACCAGATTCACTGGTGTCACTCAAGGGAGGAACTCCCTCTGGCTGAGTGACTGGGTGA  
CATCCTATAAGGTCATGGTGAGCAATGACAGCCACACGTGGGTCACTGTTAAGAATGGATCT  
GGAGACATGATATTTGAGGGAAACAGTGAGAAGGAGATCCCTGTTCTCAATGAGCTACCCGT  
CCCCATGGTGGCCCCGCTACATCCGCATAAACCTCAGTCCTGGTTTGATAATGGGAGCATCT  
GCATGAGAATGGAGATCCTGGGCTGCCCACTGCCAGATCCTAATAATTATTATCACCGCCGG  
AACGAGATGACCACCACTGATGACCTGGATTTTAAGCACCACAATTATAAGGAAATGCGCCA  
GTTGATGAAAGTTGTGAATGAAATGTGTCCCAATATCACCAAGAATTTACAACATTGGAAAAA  
GCCACCAGGGCCTGAAGCTGTATGCTGTGGAGATCTCAGATCACCTGGGGAGCATGAAGTC  
GGTGAGCCCGAGTTCCACTACATCGCGGGGGCCACGGCAATGAGGTGCTGGGCCGGGAGCT  
GCTGCTGCTGCTGGTGCAGTTCGTGTGTGAGGAGTACTTGGCCCCGAATGCGCGCATCGTCC  
ACCTGGTGGAGGAGACGCGGATTCACGTCTCCCTCCCTCAACCCCGATGGCTACGAGAAG  
GCCTACGAAGGGGGCTCGGAGCTGGGAGGCTGGTCCCTGGGACGCTGGACCCACGATGGAAT  
TGACATCAACAACAACCTTTCCTGATTTAAACACGCTGCTCTGGGAGGCAGAGGATCGACAGA  
ATGTCCCCAGGAAAGTTCCCAATCACTATATTGCAATCCCTGAGTGGTTTCTGTGCGAAAT  
GCCACGGTGGCTGCCGAGACCAGAGCAGTCATAGCCTGGATGGAAAAAATCCCTTTTGTGCT  
GGGCGGCAACCTGCAGGGCGGCGAGCTGGTGGTGGCGTATCCCTACGACCTGGTGCGGTCCC  
CCTGGAAGACGCAGGAACACACCCCCACCCCCGATGACCACGTGTTCCGCTGGCTGGCCTAC  
TCCTATGCCTCCACACACCGCCTCATGACAGACGCCCCGGAGGAGGGTGTGCCACACGGAGGA  
CTTCCAGAAGGAGGAGGGCACTGTCAATGGGGCCTCCTGGCACACCGTCGCTGGAAGTCTGA  
ACGATTTCACTACCTTCATACAACTGCTTCGAACTGTCCATCTACGTGGGCTGTGATAAA  
TACCCACATGAGAGCCAGCTGCCCCGAGGAGTGGGAGAATAACCGGGAATCTCTGATCGTGTT  
CATGGAGCAGGTTCACTGCTGGCATTAAGGCTTGGTGAGAGATTACATGGAAAAGGAATCC  
CAAACGCCATTATCTCCGTAGAAGGCATTAACCATGACATCCGAACAGCCAACGATGGGGAT  
TACTGGCGCCTCCTGAACCCTGGAGAGTATGTGGTCACAGCAAAGGCCGAAGGTTTCACTGC  
ATCCACCAAGAACTGTATGGTTGGCTATGACATGGGGGCCACAAGGTGTGACTTCACACTTA  
GCAAAACCAACATGGCCAGGATCCGAGAGATCATGGAGAAGTTTGGGAAGCAGCCCGTCAGC  
CTGCCAGCCAGGCGGCTGAAGCTGCGGGGGCGGAAGAGACGACAGCGTGGGTGACCCTCCTG  
GGCCCTTGAGACTCGTCTGGGACCCATGCAAATTAAACCAACCTGGTAGTAGCTCCATAGTG  
GACTCACTCACTGTTGTTTCTCTGTAAATTCAAGAAGTGCCTGGAAGAGAGGGTGCAATTGTG  
AGGCAGGTCCCAAAAGGGAAGGCTGGAGGCTGAGGCTGTTTTCTTTTCTTTGTTCCCATTTA  
TCCAAATAACTTGGACAGAGCAGCAGAGAAAAGCTGATGGGAGTGAGAGAACTCAGCAAGCC  
AACCTGGGAATCAGAGAGAGAAGGAGAAGGAGGGGAGCCTGTCCGTTCAGAGCCTCTGGCTGC

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**FIGURE 35B**

ATAGAAAAGGATTCTGGTGCTTCCCCTGTTTGCGTGGCAGCAAGGGTTCCACGTGCATTTGC  
AATTTGCACAGCTAAAATTGCAGCATTTCCCCAGCTGGGCTGTCCCAAATGTTACCATTTGA  
GATGCTCCCAGGCGTCCTAAGAGAATCCACCCTCTCTGGCCCTGGGACATTGCAAGCTGCTA  
CAAATAAATTCTGTGTTCTTTTGACAATAGCGTCATTGCCAAGTGCACATCAGTGAGCCTCT  
TGAATCTGTTTAGTCTCCTTTTTCAACAAAGGAGTGTGTTTCAAGAAAGGAGAGAGAGGCTGA  
GATCATTCAGGAGTTTGTGTTGGGCAGCAAGCATGGAGCTTCTTGCACAAATTCTGGGTCCATA  
AACAACCCCCAAAGTCCCTGCTGATCCAGTAGCCCTGGAGGTTCCCCAGGTAGGGAGAGCCA  
GAGGTGCCAGCCTTCCTGAAGGGCCAGAAAATTTAGCCTGGATCTCCTCTTTTACCTGCTAG  
GACTGGAAAGAGCCAGAAGTGGGGTGGCCTGAAGCCCTCTCTCTGCTTGAGGTATTGCCCT  
GTGTGGAATTGAGTGCTCATGGGTTGGCCTCATATCAGCCTGGGAGTTATTTTGTATATGTA  
GAATGCCAGATCTTCCAGATTAGGCTAAATGTAATGAAAACCTCTTAGGATTATCTGTGGAG  
CATCAGTTTGGGAAGAATTATTGAATTATCTTGCAAGAAAAAAGTATGTCTCACTTTTTGTT  
AATGTTGCTGCCTCATTGACCTGGGAAAAATGAAAAAAAAAAAAATAAAGCAAATGGTAAGACC  
CTTAAA



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**FIGURE 36**

MSRPGTATPALALVLLAVTLAGVGAQGALEDPDYYGQEIWSREPYYARPEPELETFSPPLP  
AGPGEEWERRPQEPRPPKRATKPKKAPKREKSAPEPPPPGKHSNKKVMRTKSSEKAANDDHS  
VRVAREDVRESCPPLGLETLKITDFQLHASTVKRYGLGAHRGRLNIQAGINENDFYDGAWCA  
GRNDLQQWIEVDARRLTRFTGVITQGRNSLWLSDWVTSYKVMVSNDSTWVTVKNGSGDMIF  
EGNSEKEIPVLNELPVPVMVARYIRINPQSWFDNGSICMRMEILGCPLPDPNNYYHRRNEMTT  
TDDLDFKHHNYKEMRQLMKVVNEMCPNITRIYNIGKSHQGLKLYAVEISDHPGEHEVGEPEF  
HYIAGAHGNEVLGRELLLLLVQFVCQEYLARNARIVHLVEETRIHVLPSLNPDGYEKAYEGG  
SELGGWSLGRWTHDGIDINNNFPDLNTLLWEAEDRQNVPRKVPNHYIAIPEWFLSENATVAA  
ETRAVIAWMEKIPFVLGGNLQGGELVVAYPYDLVRSPWKTQEHTPTPDDHVFRWLAYSAST  
HRLMTDARRRVCHTEDFQKEEGTVNGASWHTVAGSLNDFSYLHTNCFELSIYVGCDKYPHES  
QLPEEWENNRESLIVFMEQVHRGIKGLVRDSHGKGIPNAIISVEGINHDIRTANDGDYWRLL  
NPGEYVVTAKAEGFTASTKNCMVGYDMGATRCDFTLSTNMARIREIMEKFGKQPVSLPARR  
LKLGRGRKRRQRG

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**FIGURE 37**

CTAAGAGGACAAGATGAGGCCCGGCCTCTCATTTCTCCTAGCCCTTCTGTTCTTCCTTGGCC  
AAGCTGCAGGGGATTTGGGGGATGTGGGACCTCCAATTCCCAGCCCCGGCTTCAGCTCTTTC  
CCAGGTGTTGACTCCAGCTCCAGCTTCAGCTCCAGCTCCAGGTGCGGGCTCCAGCTCCAGCCG  
CAGCTTAGGCAGCGGAGGTTCTGTGTCCCAGTTGTTTTCCAATTTACCGGCTCCGTGGATG  
ACCGTGGGACCTGCCAGTGCTCTGTTTCCCTGCCAGACACCACCTTTCCCGTGGACAGAGTG  
GAACGCTTGGAATTCACAGCTCATGTTCTTTCTCAGAAGTTTGAGAAAGAACTTTCTAAAGT  
GAGGGAATATGTCCAATTAATTAGTGTGTATGAAAAGAACTGTTAAACCTAACTGTCCGAA  
TTGACATCATGGAGAAGGATACCATTTCTTACACTGAACTGGACTTCGAGCTGATCAAGGTA  
GAAGTGAAGGAGATGGAAAACTGGTCATACAGCTGAAGGAGAGTTTTTGGTGGAACTCAGA  
AATTGTTGACCAGCTGGAGGTGGAGATAAGAAATATGACTCTCTTGGTAGAGAAGCTTGAGA  
CACTAGACAAAAACAATGTCCTTGCCATTCGCCGAGAAATCGTGGCTCTGAAGACCAAGCTG  
AAAGAGTGTGAGGCCTCTAAAGATCAAAACACCCCTGTCTGCCACCCTCCTCCCCTCCAGG  
GAGCTGTGGTCATGGTGGTGTGGTGAACATCAGCAAACCGTCTGTGGTTCAGCTCAACTGGA  
GAGGGTTTTCTTATCTATATGGTGCTTGGGGTAGGGATTACTCTCCCCAGCATCCAAACAAA  
GGACTGTATTGGGTGGCGCCATTGAATACAGATGGGAGACTGTTGGAGTATTATAGACTGTA  
CAACACACTGGATGATTTGCTATTGTATATAAATGCTCGAGAGTTGCGGATCACCTATGGCC  
AAGGTAGTGGTACAGCAGTTTACAACAACAACATGTACGTCAACATGTACAACACCGGGAAT  
ATTGCCAGAGTTAACCTGACCACCAACACGATTGCTGTGACTCAAACCTCTCCCTAATGCTGC  
CTATAATAACCGCTTTTTCATATGCTAATGTTGCTTGGCAAGATATTGACTTTGCTGTGGATG  
AGAATGGATTGTGGGTATTATTCAACTGAAGCCAGCACTGGTAACATGGTGATTAGTAAA  
CTCAATGACACCACACTTCAGGTGCTAAACACTTGGTATACCAAGCAGTATAAACCATCTGC  
TTCTAACGCCTTCATGGTATGTGGGGTTCTGTATGCCACCCGTACTATGAACACCAGAACAG  
AAGAGATTTTTTACTATTATGACACAAACACAGGGAAAGAGGGCAAACCTAGACATTGTAATG  
CATAAGATGCAGGAAAAAGTGCAGAGCATTAACTATAACCCTTTTGACCAGAACTTTATGT  
CTATAACGATGGTTACCTTCTGAATTATGATCTTTCTGTCTTGCAGAAGCCCCAGTAAGCTG  
TTTAGGAGTTAGGGTGAAAGAGAGAAAATGTTTGTGAAAAAATAGTCTTCTCCACTTACTTAG  
ATATCTGCAGGGGTGTCTAAAAGTGTGTTCAATTTTGCAGCAATGTTTAGGTGCATAGTTCTA  
CCACACTAGAGATCTAGGACATTTGTCTTGATTTGGTGAGTTCTCTTGGGAATCATCTGCCT  
CTTCAGGCGCATTTTGCATAAAGTCTGTCTAGGGTGGGATTGTCAGAGGTCTAGGGGCACT  
GTGGGCCTAGTGAAGCCTACTGTGAGGAGGCTTCACTAGAAGCCTTAAATTAGGAATTAAGG  
AACTTAAACTCAGTATGGCGTCTAGGGATTCTTTGTACAGGAAATATTGCCCAATGACTAG  
TCCTCATCCATGTAGCACCACTAATTCTTCCATGCCTGGAAGAAACCTGGGGACTTAGTTAG  
GTAGATTAATATCTGGAGCTCCTCGAGGGACCAAATCTCCAACCTTTTTTTTTCCCCTCACTAG  
CACCTGGAATGATGCTTTGTATGTGGCAGATAAGTAAATTTGGCATGCTTATATATTCTACA  
TCTGTAAAGTGCTGAGTTTTATGGAGAGAGGCCTTTTTATGCATTAAATTGTACATGGCAA  
TAAATCCCAGAAGGATCTGTAGATGAGGCACCTGCTTTTTCTTTTCTCTCATTGTCCACCTT  
ACTAAAAGTCAGTAGAATCTTCTACCTCATAACTTCCTTCCAAAGGCAGCTCAGAAGATTAG  
AACCAGACTTACTAACCAATTCCACCCCCACCAACCCCCCTTCTACTGCCTACTTTAAAAAA  
ATTAATAGTTTTTCTATGGAACCTGATCTAAGATTAGAAAAATTAATTTTCTTTAATTTTCTTA  
TGGACTTTTATTTACATGACTCTAAGACTATAAGAAAATCTGATGGCAGTGACAAAGTGCTA  
GCATTTATTGTTATCTAATAAAGACCTTGGAGCATATGTGCAACTTATGAGTGTATCAGTTG  
TTGCATGTAATTTTTGCCTTTGTTTAAGCCTGGAACCTGTAAGAAAATGAAAATTTAATTTT  
TTTTTCTAGGACGAGCTATAGAAAAGCTATTGAGAGTATCTAGTTAATCAGTGCAGTAGTTG  
GAAACCTTGCTGGTGTATGTGATGTGCTTCTGTGCTTTTGAATGACTTTATCATCTAGTCTT  
TGTCTATTTTTTCTTTTGATGTTCAAGTCCTAGTCTATAGGATTGGCAGTTTAAATGCTTTAC  
TCCCCCTTTTAAATAAATGATTAAATGTGCTTTGAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 38**

MRPGLSFLLALLFFLGQAAGDLGDVGPPIPSPGFSSFPGVDSSSSFSSSSRSGSSSSRSLGS  
GGSVSQLFSNFTGSVDDRGTCQCSVSLPDTTFPVDRVERLEFTAHVLSQKFEKELSKVREYV  
QLISVYEKKLLNLTVRIDIMEKDTISYTELDFELIKVEVKEMEKLVIQLKESFGGSSEIVDQ  
LEVEIRNMTLLVEKLETLDKNNVLAIRREIVALKTKLKECEASKDQNTPVVHPPPTPGSCGH  
GGVNIISKPSVVQLNWRGFSYLYGAWGRDYSPOHPNKGLYWVAPLNTDGRLLLEYRLYNTLD  
DLLLYINARELRITYGQSGTAVYNNNMYVNMVNTGNIARVNLTTNTIAVTQTLPNAAAYNNR  
FSYANVAWQDIDFAVDENGLWVIYSTEASTGNMVISKLNDTTLOVLNTWYTKQYKPSASNAF  
MVCGLYATRMTNTRTEEIFYYYDTNTGKEGKLDIVMHKMQEKVQSINYNPFDQKLYVYNDG  
YLLNYDLSVLQKPQ

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**FIGURE 39**

GCTCTGAAGACCAAGCTGAAAGAGTGTGAGGCCTCTAAAGATCAAACACCCCTGTCGTCCAC  
CCTCCTCCCCTCCAGGGAGCTGTGGTCATGGTGGTGTGGTGAACATCAGCAAACCGTCTGT  
GGTTCAGCTCAACTGGAGAGGGTTTTCTTATCTATATGGTGCTTGGGGTAGGGATTACTCTC  
CCCAGCATCCAAACAAAGGNATGTATTGGGNGGCGCCATTGAATACAGATGGGAGACTGTTG  
GAGTATTATAGACTGTACAACCCACTGGATGATTTGCTATTGTATATAAATGCTCGAGAGTT  
GCGGATCACCTATGGCCAAGGTAGTGGTACAGCAGTTTACAACAACAACATGTACGTCAACA  
TGTACAACACCGGGNATATTGCCAGAGTTAACCTGACC



**FIGURE 40**

TCTCGCAGATAGTAAATAATCTCGGAAAGGCGAGAAAGAAGCTGTCTCCATCTTGTCTGTAT  
CCGCTGCTCTTGTGACGTTGTGGAGATGGGGAGCGTCCTGGGGCTGTGCTCCATGGCGAGCT  
GGATACCATGTTTGTGTGGAAGTGCCCCGTGTTTGCTATGCCGATGCTGTCCTAGTGGAAAC  
AACTCCACTGTAACTAGATTGATCTATGCACTTTTCTTGCTTGTTGGAGTATGTGTAGCTTG  
TGTAATGTTGATACCAGGAATGGAAGAACAACCTGAATAAGATTCTTGATTTTGTGAGAATG  
AGAAAGGTGTTGTCCCTTGTAACATTTTGGTTGGCTATAAAGCTGTATATCGTTTGTGCTTT  
GGTTTGGCTATGTTCTATCTTCTTCTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGA  
TCCTAGAGCTGCAGTGCACAATGGATTTTGGTTCTTTAAATTTGCTGCAGCAATTGCAATTA  
TTATTGGGGCATTCTTCATTCCAGAAGGAACCTTTTACAACCTGTGTGGTTTTATGTAGGCATG  
GCAGGTGCCTTTTGTTCATCCTCATACAACTAGTCTTACTTATTGATTTTGCACATTCATG  
GAATGAATCGTGGGTGAAAAAATGGAAGAAGGGAACCTCGAGATGTTGGTATGCAGCCTTGT  
TATCAGCTACAGCTCTGAATTATCTGCTGTCTTTAGTTGCTATCGTCCTGTTCTTTGTCTAC  
TACACTCATCCAGCCAGTTGTTTCAAGAAAACAAGGCGTTTATCAGTGTCAACATGCTCCTCTG  
CGTTGGTGCTTCTGTAATGTCTATACTGCCAAAAATCCAAGAATCACAACCAAGATCTGGTT  
TGTTACAGTCTTCAGTAATTACAGTCTACACAATGTATTTGACATGGTCAGCTATGACCAAT  
GAACCAGAAACAAATTGCAACCCAAGTCTACTAAGCATAATTGGCTACAATACAACAAGCAC  
TGTCCCAAAGGAAGGGCAGTCAGTCCAGTGGTGGCATGCTCAAGGAATTATAGGACTAATTC  
TCTTTTGTGTGTGTATTTTATTTCCAGCATCCGTACTTCAAACAATAGTCAGGTTAATAAA  
CTGACTCTAACAAGTGATGAATCTACATTAATAGAAGATGGTGGAGCTAGAAGTGATGGATC  
ACTGGAGGATGGGGACGATGTTTACCGAGCTGTAGATAATGAAAGGGATGGTGTCACTTACA  
GTTATTCCTTCTTTCACTTCATGCTTTTCTGGCTTCACTTTATATCATGATGACCCTTACC  
AACTGGTCCAGGTATGAACCCTCTCGTGAGATGAAAAGTCAGTGGACAGCTGTCTGGGTGAA  
AATCTCTTCCAGTTGGATTGGCATCGTGCTGTATGTTTGGACACTCGTGGCACCCTTGTTC  
TTACAAATCGTGATTTTGAAGTGAAGTCTAGCATGAAAGTCCCCTTTGATTATTGC  
TTATTTGAAAACAGTATTCCCAACTTTTGTAAAGTTGTGTATGTTTTTGGCTTCCCATGTAAAC  
TTCTCCAGTGTTCTGGCATGAATTAGATTTTACTGCTTGTCAATTTTGTATTTTCTTACCAA  
GTGCATTGATATGTGAAGTAGAATGAATTGCAGAGGAAAGTTTTATGAATATGGTGATGAGT  
TAGTAAAAGTGGCCATTATTGGGCTTATTCTCTGCTCTATAGTTGTGAAATGAAGAGTAAAA  
ACAAATTTGTTTGACTATTTTAAATTTATATTAGACCTTAAGCTGTTTTAGCAAGCATTA  
GCAAATGTATGGCTGCCTTTTGAATATTTGATGTGTTGCCTGGCAGGATACTGCAAAGAAC  
ATGGTTTATTTTAAATTTTATAACAAGTCACTTAAATGCCAGTTGTCTGAAAAATCTTATA  
AGGTTTTACCCTTGATACGGAATTTACACAGGTAGGGAGTGTTTAGTGGACAATAGTGTAGGTTA  
TGGATGGAGGTGTCGGTACTAAATTGAATAACGAGTAAATAATCTTACTTGGGTAGAGATGG  
CCTTTGCCAACAAAGTGAAGTGTGTTTGGTTGTTTTAACTCATGAAGTATGGGTTCAGTGGA  
AATGTTTGGAACTCTGAAGGATTTAGACAAGGTTTTGAAAAGGATAATCATGGGTTAGAAGG  
AAGTGTTTTGAAAGTCACTTTGAAAGTTAGTTTTGGGCCCAGCACGGTAGCTCACCTTGGT  
AATCCCAGCACTTTGGGAGCTTAAGTGGGTAGATTACTTGAGCCCAGGAATTCAGACCAGCT  
TGGCACATGGTGAACCTGTTCTATAAAAATAATCTGGCTTTGAGCATATGCCTGTGGTCCAG  
CACTGAGAGGCTAGTGAAGATTGCTGAGCCCAGAGCCAAAGGTTGCAGTGAGCAAGTCACGT  
CACTGCACTCTAGCTGGCACAGAGTAAGCCAAAAAATATATATATTGAAATCAAGGAGG  
CAAAATTTTGACAGGGAAGGAAGTAACTGCAAAACCACTAGGCTTTAGTAGGTACTTATATA  
AAATCTAGTCCAGTTCTCTCATTTAAAAAATGAAGACACTGAAATACAGACTTAAATAGCT  
CAGATAGCTAATTAGGAAATTTCAAGTTGGCCAATAATAGCATTCTCTGACATTTAAAAA  
TAATTTCTATTCAAAATACATGCATATTGATTTACACCTCATACTGTGATAATTAATGTGAT  
GTGGATTGCTGGTGTCCAGCATGACCCATAAACAGGTGAGAAGAATGATGGAATGTTTTAGA  
ATAAACTCCTGCTTATAGTATACTACACAGTTCAAAGATGTTTAAATGCTTTTGTATTTA  
CTGCCATGTAATTGAAATATATAGATTATTGTAACCTTTCAACCTGAAAATCAAGCAGTATG  
AGAGTTTAGTTATTTGTATGTGTCACTAGTGTCTAATGAAGCTTTTAAATCTACAATTTCT  
TCTTTAAAAATATTTATTAATGTGAATGGAATATAACAATTCAGCTTAATCCCCAACCTTA  
TTCTGTGTGTAGACATTGTATTCCACAATTTTGAATGGCTGTGTTTTACCTCTAAATAAATG  
AATTCAGAGAAAAA

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**FIGURE 41**

MGSVLGLCSMASWIPCLCGSAPCLLCRCCPSGNNSTVTRLIYALFLLVGVCVACVMLIPGME  
EQLNKIPGFCENEKGVVPCNILVGYKAVYRLCFGLAMFYLLLSLLMIKVKSSSDPRAAVHNG  
FWFFKFAAAIAIIIGAFFIPEGTFFTTVWFYVGMAGAFCFILIQVLVLLIDFAHSWNESWVEKM  
EEGNSRCWYAALLSATALNYLLSLVAIVLFFVYYTHPASCSSENKAFISVNMLLCVGASVMSI  
LPKIQESQPRSGLLQSSVITVYTMYLTSAMTNEPETNCNPSLLSIIGYNTTSTVPKEGQSV  
QWWHAQGIIGLILFLLCVFYSSIRTSNNSQVNKLTLTDESTLIEDGGARSDGSLEDGDDVH  
RAVDNERDGVITYSYSFFHFMLFLASLYIMMTLTNWSRYEPSREMKSQWTAVWVKISSSWIGI  
VLYVWTLVAPLVLTNRDFD

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**FIGURE 42**

GCGAGAAAGAAGCTGTCTCCATCTTGTCTGTATCCCGCTGCTTCTTGNGACGTTGTGGAGAT  
GGGGAGCGTCCCTGGGGCTGTGCTCCATGGCGAGCTGGATACCATGTTTGTGTGGAAGTGCC  
CCGTGTTTGCTATGCCGATGCTGTCCTAGTGGAACAANTCCACTGTAACTAGATTGATCTA  
TGCACTTTTCTTGCTTGTTGGAGTATGTGTAGCTTGTGTAATGTTGATACCAGGAATGGAAG  
AACAACTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAGGTGTTGTCCCTTGTAACATT  
TTGGTTGGCTATAAAGCTGTATATCGTTTGTGCTTTGGTTTGGCTATGTTCTATCTTCTTCT  
CTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCAGTGCACAATGGAT  
TTTGGTTCTTTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGC

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**FIGURE 43**

GTTATTGTGAACTTTGTGGAGATGGGAGGTCNTGGGGCTGTGTTCCATGGCGAGCTGGATAC  
CANGTTTGTGTGGAAGTGCCCCGTGTTTGNTATGCCGATGCTGTCCTAGTGGAACAANTCC  
ACTGTAATTAGATTGATNTATGCACTTTTNTTGCTTGTTGGAGTANGTGTAGCTTGTGTAAT  
GTTGATACCAGGAATGGAAGAACAACCTGAATAAGATTCCTGGATTTTGTGAGAATGAGAAAG  
GTGTTGTCCCTTGTAACATTTTGGTTGGCTATAAAGCTGTATATNGTTTGTGCTTTGGTTTG  
GCTANGTTCTATNTTCTTCTCTTTACTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAG  
AGCTGCAGTGCACAATGGATTTTGGTTTTTTTAAATTTGCTGCAGCAATTGCAATTATTATTG  
GGGC



**FIGURE 44**

AAGAAGCTGTCTCCATCTTGTCTGTATCCGCTGCTCTTGTGAACGTTNTGGAGATGGGGAGC  
GTCCTTGGGGTTGTGCTCCATGGCGAGCTGGATAACCATGTTTGTGTGGAAGTGCCCCGTGTT  
TGCTATGCCGATGCTGTCCTAGTGGAAACAACCTCCACTGTAAC TAGATTGATCTATGCACTT  
TTCTTGCTTGTTGGAGTATGTGTAGCTTGTGTAATGTTGATAACCAGGAATGGAAGAACAAC  
GAATAAGATTCCTGGATTTTGTGAGAATGAGAAAGGTGTTGTCCCTTGTAACATTTTGGTTG  
GCTATAAAGCTGTATATCGTTTGTGCTTTGGTTTGGCTATGTTCTATCTTCTTCTCTTTA  
CTAATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCAGTGCACAATGGATTTTGGTT  
CTTTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGC

**FIGURE 45**

GCTGTCCTTAGTGGAACAANTCCAACCTTGTAACCTTGGATTGATCTATGCACTTTTTCCTTG  
CTTGTTGGAGTATGTGTAGCTTTGTGTAATGTTGTTCCCAGGATTGGANGAACAACTGAATA  
AGATTCCTGGATTTTTGTGAGAATGAGAAAGGTGTTGTCCCCTTGTAACATTTTTGGTTGGC  
TATAAAGCTGTATATCGTTTGTGCTTTGGTTTGGCTATGTTCTATCTTCTTCTCTTTACT  
AATGATCAAAGTGAAGAGTAGCAGTGATCCTAGAGCTGCAGTGCACAATGGATTTTGGTTCT  
TTAAATTTGCTGCAGCAATTGCAATTATTATTGGGGCATTCTTCATTCCAGAAGGAACCTTTT  
ACAACTGTGTGGTTTTATGTAGGCATGGCAGGTGCCTTTTGTTCATCCTCATACAACCTAGT  
CTTACTTATTGATTTTGCACATTCATGGAATGAATCGTGGGTGAAAAAATGGAAGAAGGGA  
ACTCGAGATGTTGGTATGCAGCCTTGTTATCAGCTACAGCTCTGAATTATCTGCTGTCTTTA  
GTTGCTATCGTCCTGTTCTTTGTCTACTACACTCATCCAGCCAGTTGTTTCAGAAAACAAGGC  
GTTTCATCAGTGTCAACATGCTCCTCTGCGTTGGTGCTTCTGTAATG

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**FIGURE 46A**

CTCGGGCGCGCACAGGCAGCTCGGTTTGCCCTGCGATTGAGCTGCGGGTTCGCGGCCGGCGCC  
GGCTCTCCAATGGCAAATGTGTGTGGCTGGAGGCGAGCGCGAGGCTTTCGGCAAAGGCAGT  
CGAGTGTTCGAGACCGGGGCGAGTCCTGTGAAAGCAGATAAAAGAAAACATTTATTAACGT  
GTCATTACGAGGGGAGCGCCCGGGGGCTGTCGCACTCCCCGCGGAACATTTGGCTCCCT  
CCAGCTCCGAGAGAGGAGAAGAAGAAAGCGGAAAAGAGGCAGATTCACGTCGTTTCCAGCCA  
AGTGGACCTGATCGATGGCCCTCCTGAATTTATCACGATATTTGATTTATTAGCGATGCCCC  
CTGGTTTGTGTGTACGCACACACACGTGCACACAAGGCTCTGGCTCGCTTCCCTCCCTCGT  
TTCCAGCTCCTGGGCGAATCCCACATCTGTTTCAACTCTCCGCCGAGGGCGAGCAGGAGCGA  
GAGTGTGTCGAATCTGCGAGTGAAGAGGGACGAGGGAAAAGAAACAAAGCCACAGACGCAAC  
TTGAGACTCCCGCATCCCAAAGAAGCACCAGATCAGCAAAAAAAGAAGATGGGCCCCCGA  
GCCTCGTGCTGTGCTTGCTGTCCGCAACTGTGTTCTCCCTGCTGGGTGGAAGCTCGGCCTTC  
CTGTGCGACCACCGCCTGAAAGGCAGGTTTCAGAGGGACCGCAGGAACATCCGCCCCAACAT  
CATCCTGGTGCTGACGGACGACCAGGATGTGGAGCTGGGTTCATGCAAGTGATGAACAAGA  
CCCGGCGCATCATGGAGCAGGGCGGGGCGCACTTCATCAACGCCTTCGTGACCACACCCATG  
TGCTGCCCCCTACGCTCCTCCATCCTCACTGGCAAGTACGTCCACAACCACAACACCTACAC  
CAACAATGAGAACTGCTCCTCGCCCTCCTGGCAGGCACAGCACGAGAGCCGCACCTTTGCCG  
TGTAACCTCAATAGCACTGGCTACCGGACAGCTTTCTTCGGGAAGTATCTTAATGAATACAAC  
GGCTCCTACGTGCCACCCGGCTGGAAGGAGTGGGTTCGGAATCCTTAAAAACTCCCGCTTTTA  
TAACTACACGCTGTGTTCGGAACGGGGTGAAAGAGAAGCACGGCTCCGACTACTCCAAGGATT  
ACCTCACAGACCTCATCACCAATGACAGCGTGAGCTTCTTCGCGACGTCCAAGAAGATGTAC  
CCGCACAGGCCAGTCCTCATGGTCATCAGCCATGCAGCCCCCACGGCCCTGAGGATTCAGC  
CCCACAATATTCACGCCTCTTCCCAAACGCATCTCAGCACATCAGCCGAGCTACAACCTACG  
CGCCCAACCCGGACAAACACTGGATCATGCGCTACACGGGGCCCATGAAGCCCATCCACATG  
GAATTCACCAACATGCTCCAGCGGAAGCGCTTGACAGACCCTCATGTGCGGTGGACGACTCCAT  
GGAGACGATTTACAACATGCTGGTTGAGACGGGCGAGCTGGACAACACGTACATCGTATACA  
CCGCCGACCACGGTTACCACATCGGCCAGTTTGGCCTGGTGAAAGGGAAATCCATGCCATAT  
GAGTTTGACATCAGGGTCCCGTTCTACGTGAGGGGCCCCAACGTGGAAGCCGGCTGTCTGAA  
TCCCCACATCGTCCTCAACATTGACCTGGCCCCCACCATCCTGGACATTGCAGGCCTGGACA  
TACCTGCGGATATGGACGGGAAATCCATCCTCAAGCTGCTGGACACGGAGCGGCCGGTGAAT  
CGGTTCCTACTTGAAAAAGAAGATGAGGGTCTGGCGGGACTCCTTCTTGGTGGAGAGAGGCAA  
GCTGCTACACAAGAGAGACAATGACAAGGTGGACGCCAGGAGGAGAACTTTCTGCCCAAGT  
ACCAGCGTGTGAAGGACCTGTGTCAGCGTGCTGAGTACCAGACGGCGTGTGAGCAGCTGGGA  
CAGAAGTGGCAGTGTGTGGAGGACGCCACGGGGAAGCTGAAGCTGCATAAGTGCAAGGGCCC  
CATGCGGCTGGGCGGCAGCAGAGCCCTCTCCAACCTCGTGCCCAAGTACTACGGGCAGGGCA  
GCGAGGCCTGCACCTGTGACAGCGGGGACTACAAGCTCAGCCTGGCCGGACGCCGGAAAAAA  
CTCTTCAAGAAGAAGTACAAGGCCAGCTATGTCCGCAAGTCGCTCCATCCGCTCAGTGGCCAT  
CGAGGTGGACGGCAGGGTGTACCACGTAGGCCTGGGTGATGCCGCCAGCCCCGAAACCTCA  
CCAAGCGGCACTGGCCAGGGGCCCCCTGAGGACCAAGATGACAAGGATGGTGGGGACTTCAGT  
GGCACTGGAGGCCTTCCCGACTACTCAGCCGCCAACCCCATTAAGTGACACATCGGTGCTA  
CATCCTAGAGAACGACACAGTCCAGTGTGACCTGGACCTGTACAAGTCCCTGCAGGCCTGGA  
AAGACCACAAGCTGCACATCGACCACGAGATTGAAACCCTGCAGAACAATAAAGAACCTG  
AGGGAAGTCCGAGGTACCTGAAGAAAAAGCGGCCAGAAGAATGTGACTGTCACAAAATCAG  
CTACCACACCCAGCACAAAGGCCGCTCAAGCACAGAGGCTCCAGTCTGCATCCTTTTCAGGA  
AGGGCCTGCAAGAGAAGGACAAGGTGTGGCTGTTGCGGGAGCAGAAGCGCAAGAAGAACTC  
CGCAAGCTGCTCAAGCGCCTGCAGAACAACGACACGTGCAGCATGCCAGGCCTCACGTGCTT  
CACCCACGACAACCAGCACTGGCAGACGGCGCCTTTCTGGACACTGGGGCCTTTCTGTGCCT  
GCACCAGCGCCAACAATAACACGTACTGGTGCATGAGGACCATCAATGAGACTCACAATTC

**FIGURE 46B**

CTCTTCTGTGAATTTGCAACTGGCTTCCTAGAGTACTTTGATCTCAACACAGACCCCTACCA  
GCTGATGAATGCAGTGAACACACTGGACAGGGATGTCCTCAACCAGCTACACGTACAGCTCA  
TGGAGCTGAGGAGCTGCAAGGGTTACAAGCAGTGTAACCCCCGGACTCGAAACATGGACCTG  
GATGGAGGAAGCTATGAGCAATACAGGCAGTTTCAGCGTCGAAAGTGGCCAGAAATGAAGAG  
ACCTTCTTCCAAATCACTGGGACAACCTGTGGGAAGGCTGGGAAGGTTAAGAAACAACAGAGG  
TGGACCTCCAAAAACATAGAGGCATCACCTGACTGCACAGGCAATGAAAAACCATGTGGGTG  
ATTTCCAGCAGACCTGTGCTATTGGCCAGGAGGCCTGAGAAAGCAAGCACGCACTCTCAGTC  
AACATGACAGATTCTGGAGGATAACCAGCAGGAGCAGAGATAACTTCAGGAAGTCCATTTTT  
GCCCCTGCTTTTGCTTTGGATTATACCTCACCAGCTGCACAAAATGCATTTTTTTCGTATCAA  
AAAGTCACCACTAACCCTCCCCCAGAAGCTCACAAAGGAAAACGGAGAGAGCGAGCGAGAGA  
GATTCCTTGGAATTTCTCCCAAGGGCGAAAGTCATTGGAATTTTAAATCATAGGGGAAA  
AGCAGTCCTGTTCTAAATCCTCTTATTCTTTTGGTTTGTACAAAGAAGGAACCTAAGAAGCA  
GGACAGAGGCAACGTGGAGAGGCTGAAAACAGTGCAGAGACGTTTGACAATGAGTCAGTAGC  
ACAAAAGAGATGACATTTACCTAGCACTATAAACCCCTGGTTGCCTCTGAAGAACTGCCTTC  
ATTGTATATATGTGACTATTTACATGTAATCAACATGGGAACTTTTAGGGGAACCTAATAAG  
AAATCCCAATTTTCAGGAGTGGTGGTGTCAATAAACGCTCTGTGGCCAGTGTAAGAAAAA



**FIGURE 47**

MGPPSLVLCLLSATVFSLLGGSSAFLSHHRLKGRFQDRRNIRPNIILVLTDDQDVELGSMQ  
VMNKTRRIMEQGGAHFINAFVTTPMCCPSRSSILTGKYVHNHNTYTNNECSPSWQAQHE  
RTFAVYLNSTGYRTAFFGKYLNEYNGSYVPPGWKEWVGLLKNSRFYNYTLCRNGVKEKHGSD  
YSKDYLTDLITNDSVSFFRTSKKMYPHRPVLMVISHAAPHGPEDSAPQYSRLFPNASQHITP  
SYNYAPNPDKHWIMRYTGPMKPIHMEFTNMLQRKRLQTLMSVDDSMETIYNMLVETGELDNT  
YIVYTADHGYHIGQFGLVKGKSMPYEFDIRVPFYVRGPNVEAGCLNPHIVLNIDLAPTILDI  
AGLDIPADMKGKSILKLLDTERPVNRFHLKKKMRVWRDSFLVERGKLLHKRDNDKVDAQEEN  
FLPKYQRVKDLCQRAEYQTACEQLGQKWQCVEDATGKLKLHKCKGPMRLGGSRALSNLVPKY  
YGQGSEACTCDSGDYKLSLAGRRKKLFKKKYKASYVRSRSIRSVVAIEVDGRVYHVGLGDAAQ  
PRNLTKRHWPGAPEDQDDKDGGDFSGTGGLPDYSAANPIKVTHRCYILENDTVQCDLDLYKS  
LQAWKDHKLHIDHEIETLQNKIKNLREVRGHLKKKRPEECDCHKISYHTQHKGRLKHRGSSL  
HPFRKGLQEKDKVWLLREQKRKKKLRKLLKRLQNNDTCSMPGLTCFTHDNQHWQTAPFWTLG  
PFCACTSANNNTYWCMTINETHNFLFCEFATGFLEYFDLNTDPYQLMNAVNTLDRDVLNQL  
HVQLMELRSCKGYKQCNPRTRNMDLDGGSYEQYRQFQRRKWPEMKRPSSKSLGQLWEGWEG

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**FIGURE 48**

AACAAAGTTCAGTGACTGAGAGGGCTGAGCGGAGGCTGCTGAAGGGGAGAAAGGAGTGAGGA  
GCTGCTGGGCAGAGAGGGACTGTCCGGCTCCCAGATGCTGGGCCTCCTGGGGAGCACAGCCC  
TCGTGGGATGGATCACAGGTGCTGCTGTGGCGGTCTGCTGCTGCTGCTGCTGCTGGCCACC  
TGCCTTTTCCACGGACGGCAGGACTGTGACGTGGAGAGGAACCGTACAGCTGCAGGGGGAAA  
CCGAGTCCGCCGGGCCCAGCCTTGGCCCTTCCGGCGGCGGGGCCACCTGGGAATCTTTCACC  
ATCACCGTCATCCTGGCCACGTATCTCATGTGCCGAATGTGGGCCTCCACCACCACCACCAC  
CCCCGCCACACCCCTCACCACTCCACCACCACCACCACCCCCACCGCCACCATCCCCGCCA  
CGCTCGCTTGAGGCTGCTGTGCGCCGGTGCCTGTGGACAGCAGCTGCCCCCTGCCCTCCCATCTG  
TTCCCAGGACAAGTGGACCCCATGTTTCCATGTGGAAGGATGCATCTCTGGGGTGAACGAGG  
GGAACAATAGACTGGGGCTTGCTCCAGCTGCATTTGCATGGCATGCCCCAGTGTACTATGGC  
AGCAGAGAATGGAGGAACACTGGGTCTGCAGTGCTGAAGGGTTTGGGGAGTGGAGAGCAAGG  
GTGCTCTTTCGGGGCTGGACAGCCCGTCTTGACAGTGACTCCCAGTGAGCCCCAGAAATG  
ACAAGCGTGTCTTGGCAGAGCCAGCACACAAGTGGATGTGAAGTGCCCGTCTTGACCTCCTC  
ATCAGGCTGCTGCAGGCCTCTGGCGGGCAGGGCACTGGGAGAGGCCCTGAGAATGTCCTTTT  
GGTTTGGAGAAGGCAGTGTGAGGCTGCACAGTCAATTCATCGGTGCCTTAGTCCAAGAAAAT  
AAAAACCACTAAGAAGCTTTAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 49**

MLGLLGSTALVGWITGA AVAVLLLLLLLLLATCLFHGRQDCDVERNRTAAGGNRVRRAPWPFR  
RRGHLGIFHHHRHPGHVSHV PNVGLHHHHHPRHTPHHLHHHHHPHRHHPRHAR

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**FIGURE 50**

GGCGGCTGCTGAGCTGCCTTGAGGTGCAGTGTTGGGGATCCAGAGCCATGTCGGACCTGCTA  
CTACTGGGCCTGATTGGGGGCCTGACTCTCTTACTGCTGCTGACGCTGCTGGCCTTTGCCGG  
GTACTCAGGGCTACTGGCTGGGGTGGAAGTGAGTGCTGGGTCACCCCCCATCCGCAACGTCA  
CTGTGGCCTACAAGTTCCACATGGGGCTCTATGGTGAGACTGGGCGGCTTTTCACTGAGAGC  
TGCAGCATCTCTCCCAAGCTCCGCTCCATCGCTGTCTACTATGACAACCCCCACATGGTGCC  
CCCTGATAAGTGCCGATGTGCCGTGGGCAGCATCCTGAGTGAAGGTGAGGAATCGCCCTCCC  
CTGAGCTCATCGACCTCTACCAGAAATTTGGCTTCAAGGTGTTCTCCTTCCCGGCACCCAGC  
CATGTGGTGACAGCCACCTTCCCCTACACCACCATTCTGTCCATCTGGCTGGCTACCCGCCG  
TGTCCATCCTGCCTTGGACACCTACATCAAGGAGCGGAAGCTGTGTGCCTATCCTCGGCTGG  
AGATCTACCAGGAAGACCAGATCCATTTTCATGTGCCCACTGGCACGGCAGGGAGACTTCTAT  
GTGCCTGAGATGAAGGAGACAGAGTGGAATGGCGGGGGCTTGTGGAGGCCATTGACACCCA  
GGTGGATGGCACAGGAGCTGACACAATGAGTGACACGAGTTCTGTAAGCTTGGAAGTGAGCC  
CTGGCAGCCGGGAGACTTCAGCTGCCACACTGTCACCTGGGGCGAGCAGCCGTGGCTGGGAT  
GACGGTGACACCCGCAGCGAGCACAGCTACAGCGAGTCAGGTGCCAGCGGCTCCTCTTTTGA  
GGAGCTGGACTTGGAGGGCGAGGGGCCCTTAGGGGAGTCACGGCTGGACCCTGGGACTGAGC  
CCCTGGGGACTACCAAGTGGCTCTGGGAGCCCACTGCCCCCTGAGAAGGGCAAGGAGTAACCC  
ATGGCCTGCACCCTCCTGCAGTGCAGTTGCTGAGGAACTGAGCAGACTCTCCAGCAGACTCT  
CCAGCCCTCTTCCTCCTTCCTCTGGGGGAGGAGGGGTTCTTGAGGGACCTGACTTCCCCTGC  
TCCAGGCCTCTTGCTAAGCCTTCTCCTCACTGCCCTTTAGGCTCCCAGGGCCAGAGGAGCCA  
GGGACTATTTTCTGCACCAGCCCCCAGGGCTGCCGCCCTGTTGTGTCTTTTTTTTCAGACTC  
ACAGTGGAGCTTCCAGGACCCAGAATAAAGCCAATGATTTACTTGTTTCACCTGGAAAAAA  
AAAAA



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**FIGURE 51**

MSDLLLLGLIGGLTLLLLLLTLLAFAGYSGLLAGVEVSAGSPPIRNVTVAYKFHMGLYGETGR  
LFTESCSISPKLRSIAYYYDNPHMVPPDKCRCAVGSILSEGEESPSPELIDLYQKFGFKVFS  
FPAPSHVVTATFPYTTILSIWLATTRVHPALDTYIKERKLCAYPRLEIYQEDQIHFMCPAR  
QGDFYVPEMKETEWKWRGLVEAIDTQVDGTGADTMSDTSSVSLEVSPGSRETSAAATLSPGAS  
SRGWDDGDTRSEHSYSESGASGSSFEELDLEGEGLGESRLDPGTEPLGTTKWLWEPTAPEKGKE

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**FIGURE 52**

CCGCGGGAACGCTGTCCTGGCTGCCGCCACCCGAACAGCCTGTCCTGGTGCCCCGGCTCCCT  
GCCCCGCGCCCAGTCATGACCCTGCGCCCCCTCACTCCTCCCGCTCCATCTGCTGCTGCTGCT  
GCTGCTCAGTGCGGCGGTGTGCCGGGCTGAGGCTGGGCTCGAAACCGAAAGTCCCGTCCGGA  
CCCTCCAAGTGGAGACCCTGGTGGAGCCCCCAGAACCATGTGCCGAGCCCGCTGCTTTTGGA  
GACACGCTTCACATACTACACGGGAAGCTTGGTAGATGGACGTATTATTGACACCTCCCT  
GACCAGAGACCCTCTGGTTATAGAACTTGGCCAAAAGCAGGTGATTCCAGGTCTGGAGCAGA  
GTCTTCTCGACATGTGTGTGGGAGAGAAGCGAAGGGCAATCATTCCTTCTCACTTGGCCTAT  
GGAAAACGGGGATTTCCACCATCTGTCCCAGCGGATGCAGTGGTGCAGTATGACGTGGAGCT  
GATTGCACTAATCCGAGCCAACCTACTGGCTAAAGCTGGTGAAGGGCATTTTGCCTCTGGTAG  
GGATGGCCATGGTGCCAGCCCTCCTGGGCCTCATTGGGTATCACCTATACAGAAAGGCCAAT  
AGACCCAAAGTCTCCAAAAAGAAGCTCAAGGAAGAGAAACGAAACAAGAGCAAAAAGAAATA  
ATAAATAATAAATTTTAAAAAACTTAAAAA

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**FIGURE 53**

MTLRPSLLPLHLLLLLLLLSAAVCRAEAGLETESPVRTLQVETLVEPPEPCAEPAAFGDTLHI  
HYTGSLVDGRIIDTSLTRDPLVIELGQKQVIPGLEQSLDMCVGEKRRAIIPSHLAYGKRGF  
PPSVPADAVVQYDVELIALIRANYWLKLVKGILPLVGMAMVPALLGLIGYHLYRKANRPKVS  
KKKLKEEKRNKSKKK

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**FIGURE 54**

CCCGGGAACGTGTTCCCTGGCTGCCGCACCCGAACAGCCTGTCCTGGTGCCCCGGCTCCCTGC  
CCCGCGCCCAGTCATGACCCTGCGCCCCTCACTCCTCCCGCTCCATCTGCTGCTGCTGCTGC  
TGCTCAGTGCGGCGGTGTGCCGGGCTGAGGCTGGGCTCGAAACCGAAAGTCCCGTCCGGACC  
CTCCAAGTGGAGACCCTGGTGGAGCCCCCAGAACCATGTGCCGAGCCCGCTGCTTTTGGAGA  
CACGCTTCACATACTACACGGGAAGCTTGGTAGATGGACGTATTATTGACACCTCCCTGA  
CCAGAGACCCTCTGGTTATAGAACTTGGCCAAAAGCAGGTGATTCCAGGTCTGGAGCAGAGT  
CTTCTCGACATGTGTGTGGGAGAGAAGCGAAGGGCAATCATTCTTCTCACTTGGCCTATGG  
AAAACGGGGATTTCACCATCTGTCCCAGCGGATGCAGTGGTGCAGTATGACGTGGAGCTGA  
TTGCACTAATCCGAGCCAACTACTGGCTAAAGCTGGTGAAGGGCATTTTGCCTCTGGTAGGG  
ATGGCCATGGTGCCACCCTCCTGGGCCTCATTGGGTATCACCTATACAGAAAGGCCAATAGA  
CCCAAAGTCTCCAAAAGAAGCTCAAGGAAGAGAAACGAAACAAGAGCAAAAAGAAATAATA  
AATAATAAATTTTAAAAAACTTA



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**FIGURE 55**

CCGAAAGTCCCGTCCGGACCCTCCAAGTGGAGACCCTGGTGGAGCCCCCAGAACCATGTGCC  
GAGCCCGCTGCTTTTGGAGACACGCTTCACATACTACACGGGAAGCTTGGTAGATGGACG  
TATTATTGACACCTCCCTGACCAGAGACCCTCTGGTTATAGAAGTTGGCCAAAAGCAGGTGA  
TTCCAGGTCTGGAGCAGAGTCTTCTCGACATGTGTGTGGGAGAGAAGCGAAGGGCAATCATT  
CCTTCTCACTTGGCCTATGGAAAACGGGGATTTCCACCATCTGTCCCAGCGGATGCAGTGGT  
GCAGTATGACGTGGAGCTGATTGCACTAATCCGAGCCAACACTGGCTAAAGCTGGTGAAGG  
GCATTTTGCCTCTGGTAGGGATGGCCATGGTGCCAGCCCTCCTGGGCCTCATTGGGTATCAC  
CTATACAGAAAGGCCAATAGACCCAAAGTCTCCAAAAGAAGCTCAAGGAAGAGAAACGAAA  
CAAGAGCAAAAAGAAATAATAATAATAAATTTTAAAAAACTTAAAA

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**FIGURE 56**

CTGCTGCATCCGGGTGTCTGGAGGCTGTGGCCGTTTTGTTTTCTTGGCTAAAATCGGGGGAG  
TGAGGCGGGCCGGCGCGGCGGACACCGGGCTCCGGAACCACTGCACGACGGGGCTGGACTG  
ACCTGAAAAAAATGTCTGGATTTCTAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGG  
GAAAAGCGCAATACTATTGCTTCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGGTGGAT  
TATCATAGATGCAGCTGTTATTTATCCCACCATGAAAGATTTCAACCACTCATACCATGCCT  
GTGGTGTTATAGCAACCATAGCCTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGA  
GGTGATAGTTACAGTGAAGGTTGTCTGGGTCAAACAGGTGCTCGCATTGGCTTTTCGTTGG  
TTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTTGGAGGTTATGTTG  
CTAAAGAAAAAGACATAGTATACCCTGGAATTGCTGTATTTTTTCCAGAATGCCTTCATCTTT  
TTTGGAGGGCTGGTTTTTTAAGTTTGGCCGCACTGAAGACTTATGGCAGTGAACACATCTGAT  
TTCCCACAGCACAAACAGCCCTGCATGGGTTTGTTTGTTTTTTTTACTGCTCACTCCCAACCTT  
TTGTAATGCCATTTTCTAAACTTATTTCTGAGTGTAGTCTCAGCTTAAAGTTGTGTAATACT  
AAAATCACGAGAACACCTAAACAACAACCAAAAATCTATTGTGGTATGCACTTGATTAACCTT  
ATAAAATGTTAGAGGAACTTTCACATGAATAATTTTTGTCAAATTTTATCATGGTATAATT  
TGTA AAAATAAAAAGAAATTACAAAAGAAATTATGGATTTGTCAATGTAAGTATTTGTCATA  
TCTGAGGTCCAAAACCACAATGAAAGTGCTCTGAAGATTTAATGTGTTTATTCAAATGTGGT  
CTCTTCTGTGTCAAATGTTAAATGAAATATAAACATTTTTTTAGTTTTTTAAAATATTCCGTGG  
TCAAATTCCTCCTCACTATAATTGGTATTTACTTTTACCAAAAATTCTGTGAACATGTAAT  
GTA ACTGGCTTTTGAGGGTCTCCCAAGGGGTGAGTGGACGTGTTGGAAGAGAGAAGCACCAT  
GGTCCAGCCACCAGGCTCCCTGTGTCCCTTCCATGGGAAGGTCTTCCGCTGTGCCTCTCATT  
CCAAGGGCAGGAAGATGTGACTCAGCCATGACACGTGGTTCTGGTGGGATGCACAGTCACTC  
CACATCCACCACTG

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**FIGURE 57**

MSGFLEGLRCSECIDWGEKRNTIASIAAGVLFFTGWIIIDA AVIYPTMKDFNHSYHACGVI  
ATIAFLMINAVSNGQVRGDSYSEGCLGQTGARIWLFVGFMLAFGSLIASMWILFGGYVAKEK  
DIVYPGIAVFFQNAFIFFGGLVFKFGRTEDLWQ

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**FIGURE 58**

TTCTTGGCTAAAATCGGGGGAGTGAGGCGGGCCGGCGCGGCGGACACCGGGCTCCGGAACC  
ACTGCACGACGGGGCTGGACTGACCTGAAAAAATGTCTGGATTTCTAGAGGGCTTGAGATG  
CTCAGAATGCATTGACTGGGGGGAAAAGCGCAATACTATTGCTTCCATTGCTGCTGGTGTAC  
TATTTTTTTACAGGCTGGTGGATTATCATAGATGCAGCTGTTATTTATCCCACCATGAAAGAT  
TTCAACCACTCATACCATGCCTGTGGTGTATAGCAACCATAGCCTTCCTAATGATTAATGC  
AGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTTGTCTGGGTCAAACAGGTG  
CTCGCATTGCTTTTCGTTGGTTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGG  
ATTCTTTTTTGGAGGTTATGTTGCTAAAGAAAAAGACATAGTATACCCTGGAATTGCTGTATT  
TTCCAGAATGCCTTCATCTTTTTTGGAGGGCTGGTTTTTTAAGTTTGGC



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**FIGURE 59**

TGGACGGACCTGAAAAAATGTTTGGATTNTAGAGGGNTTGAGATG TTCAGAATGCATGAC  
TGGGGGAAAAGCGCAAATACTATTGCTTCCATTGCTGCTGGTGTANTATTTTTTACAGGCTG  
GTGGATTATCATAGATGCAGNTGTTATTTATCCCACCATGAAAGATTTCAACCANTCATACC  
ATGCCTGTGGTGTTATAGCAACCATAGCCTTCNTAATGATTAATGCAGTATCGAATGGACAA  
GTCCGAGGTGATAGTTACAGTGAAGGTTGTTTGGGTCAAACAGGTGCTCGCATTTGGCTTTT  
CGTTGGTTTCATGTTGGCCTTTGGATCTCTGATTGCATCTATGTGGATTCTTTTTTGGAGGTT  
ATGTTGCTAAAGAAAAAGACATAGTATACCCTGGAATTGNTGTATTTTTTCCAGAATGCCTTC  
ATCTTTTTTTGGAGGGCTGGTTTTTTAAGTTTGGCCGCACTGAAGANTTATGGCAGTG

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**FIGURE 60**

GGACACCGGGTTCCGGACCAATGCANGACGGGGTGGANTGACCTGAAAAAATGTTTGGATT  
TTTAGAGGGCTTGAGATGNTCAGAATGCATTGACTGGGGGAAAAGCGCAATANTATTGCTTT  
CCATTGCTGCTGGTGTACTATTTTTTACAGGGTGGTGGATTATCATAGATGCAGCTGTTATT  
TATCCCACCATGAAAGATTTNAACCACTCATACCATGCCTGTGGTGTTATAGCAACCATAGC  
CTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTT  
GTTTGGGTCAAACAGGTGNTCGCATTGCTTTTCGTTGGTTTCATGTTGGCCTTTGGATTT  
CTGATTGNATTCTATGCGGATTCTTCTTGGAGGTTATGTTGCTAAAGAAAAAGACATAGTAT  
ACCCTGGAATTNCTNTATTTTTCCAGAATGCC

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**FIGURE 61**

TAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGGGAAAAGCGCAATANTATTGCTTCC  
ATTGNTGNTGGTGTANTATTTTTTTTACAGGCTGGTGGATTATNATAGATGCAGCTGTTATTT  
ATCCCACCATGAAAGATTTNAACCANTCATACCATGCCTGTGGTGTATAGCAACCATAGCC  
TTCCTAATGATTAATGCAGTATNGAATGGACAAGTCCGAGGTGATAGTTACAGTGAAGGTTG  
TTTGGGTCAAACAGGTGNTNGCATTTGGCTTTTNGTTGGTTTCATGTTGGCCTTTGGATCTN  
TGATTGCATTTATGTGGATTNTTTTTTGGAGGTTATGTTGCTAAAGNAAAAGACATAGTATAC  
CCTGT

**FIGURE 62**

GGGAGGCTGTGNCCGTTTTGTTTTNTTGGCTAAAATCGGGGGAGTGAGGCGGCCCGGCGCGG  
CGNGACACCGGGTTCCGGGAACCATTCACGACGGGGTGGACTGACCTGAAAAAATGTTTG  
GATTTNTAGAGGGCTTGAGATGCTCAGAATGCATTGACTGGGGGGAAAAGCGCAATACTATT  
GCTTCCATTGCTGCTGGTGTACTATTTTTTACAGGCTGGTGGATTATCATAGATGCAGCTGT  
TATTTATCCCACCATGAAAGATTTCAACCACTCATACCATGCCTGTGGTGTTATAGCAACCA  
TAGCCTTCCTAATGATTAATGCAGTATCGAATGGACAAGTCCGAGGTGATAGTTACAGTGAA  
GGTTGTCTGGGTCAAACAGGTGCTCGCATTGGCTTTTCGTTGGTTTCATGTTGGCCTTTGG  
ATNTCTGATTGCATCTATGTGGATTCTTTTTTGGAGGTTATGTTGCTAAAGAAAAAGACATAG  
TATACCCTGGAATTGCTGTATTTTTTCCAGAATGCCTTCATNTTTTTTGGAGGGCTG



**FIGURE 63**

CGACGCCGGCGTGATGTGGCTTCCGCTGGTGCTGCTCCTGGCTGTGCTGCTGCTGGCCGTCC  
TCTGCAAAGTTTACTTGGGACTATTCTCTGGCAGCTCCCCGAATCCTTTCTCCGAAGATGTC  
AAACGGCCCCCAGCGCCCCCTGGTAACTGACAAGGAGGCCAGGAAGAAGGTTCTCAAACAAGC  
TTTTTCAGCCAACCAAGTGCCGGAGAAGCTGGATGTGGTGGTAATTGGCAGTGGCTTTGGGG  
GCCTGGCTGCAGCTGCAATTCTAGCTAAAGCTGGCAAGCGAGTCCTGGTGCTGGAACAACAT  
ACCAAGGCAGGGGGCTGCTGTCATACCTTTGGAAAGAATGGCCTTGAATTTGACACAGGAAT  
CCATTACATTGGGCGTATGGAAGAGGGCAGCATTGGCCGTTTTATCTTGGACCAGATCACTG  
AAGGGCAGCTGGACTGGGCTCCCCTGTCCTCTCCTTTTGACATCATGGTACTGGAAGGGCCC  
AATGGCCGAAAGGAGTACCCCATGTACAGTGGAGAGAAAGCCTACATTCAGGGCCTCAAGGA  
GAAGTTTCCACAGGAGGAAGCTATCATTGACAAGTATATAAAGCTGGTTAAGGTGGTATCCA  
GTGGAGCCCCCTCATGCCATCCTGTTGAAATTCCTCCCATTGCCCGTGGTTCAGCTCCTCGAC  
AGGTGTGGGCTGCTGACTCGTTTCTCTCCATTCTTCAAGCATCCACCCAGAGCCTGGCTGA  
GGTCTGTCAGCAGCTGGGGGGCCTCCTCTGAGCTCCAGGCAGTACTCAGCTACATCTTCCCCA  
CTTACGGTGTCAACCCCAACACAGTGCCTTTTCCATGCACGCCCTGCTGGTCAACCACTAC  
ATGAAAGGAGGCTTTTATCCCCGAGGGGGTTCAGTGAAATTGCCTTCCACACCATCCCTGT  
GATTGAGCGGGCTGGGGGGCGCTGTCTCACAAAGGCCACTGTGCAGAGTGTGTTGCTGGACT  
CAGCTGGGAAAGCCTGTGGTGTGAGTGTGAAGAAGGGGCATGAGCTGGTGAACATCTATTGC  
CCCATCGTGGTCTCCAACGCAGGACTGTTCAACACCTATGAACACCTACTGCCGGGGGAACGC  
CCGCTGCCTGCCAGGTGTGAAGCAGCAACTGGGGACGGTGCGGCCCCGGCTTAGGCATGACCT  
CTGTTTTTCATCTGCCTGCGAGGCACCAAGGAAGACCTGCATCTGCCGTCCACCAACTACTAT  
GTTTACTATGACACGGACATGGACCAGGCGATGGAGCGCTACGTCTCCATGCCCAGGGGAAGA  
GGCTGCGGAACACATCCCTCTTCTCTTCTTCTCGCTTTCCCATCAGCCAAAGATCCGACCTGGG  
AGGACCGATTCCCAGGCCGGTCCACCATGATCATGCTCATACCCACTGCCTACGAGTGGTTT  
GAGGAGTGGCAGGCGGAGCTGAAGGGAAAGCGGGGCAGTGACTATGAGACCTTCAAAAATC  
CTTTGTGGAAGCCTCTATGTGAGTGGTCTGAAACTGTTCCACAGCTGGAGGGGAAGGTGG  
AGAGTGTGACTGCAGGATCCCCACTCACCAACCAGTTCTATCTGGCTGCTCCCCGAGGTGCC  
TGCTACGGGGCTGACCATGACCTGGGGCCGCTGCACCCTTGTGTGATGGCCTCCTTGAGGGC  
CCAGAGCCCCATCCCCAACCTCTATCTGACAGGCCAGGATATCTTACCTGTGGACTGGTCG  
GGGCCCTGCAAGGTGCCCTGCTGTGCAGCAGCGCCATCCTGAAGCGGAACCTTGTAATCAGAC  
CTTAAGAATCTTGATTCTAGGATCCGGGCACAGAAGAAAAAGAATTAGTTCCATCAGGGAGG  
AGTCAGAGGAATTTGCCCAATGGCTGGGGCATCTCCCTTGACTTACCCATAATGTCTTTCTG  
CATTAGTTCCTTGACAGTATAAAGCACTCTAATTTGGTTCTGATGCCTGAAGAGAGGCCTAG  
TTTAAATCACAATTCCGAATCTGGGGCAATGGAATCACTGCTTCCAGCTGGGGCAGGTGAGA  
TCTTTACGCCTTTTATAACATGCCATCCCTACTAATAGGATATTGACTTGGATAGCTTGATG  
TCTCATGACGAGCGGCGCTCTGCATCCCTCACCCATGCCTCCTAACTCAGTGATCAAAGCGA  
ATATTCCATCTGTGGATAGAACCCTGGCAGTGTTGTGAGCTCAACCTGGTGGGTTCAGTTC  
TGTCCTGAGGCTTCTGCTCTCATTCAATTTAGTGCTACGCTGCACAGTTCTACACTGTCAAGG  
GAAAAGGGAGACTAATGAGGCTTAACTCAAACCTGGGGCGTGGTTTTGGTTGCCATTCCATA  
GGTTTGGAGAGCTCTAGATCTCTTTTGTGCTGGGTTCAGTGGCTCTTCAGGGGACAGGAAAT  
GCCTGTGTCTGGCCAGTGTGGTTCTGGAGCTTTGGGGTAACAGCAGGATCCATCAGTTAGTA  
GGGTGCATGTGAGATGATCATATCCAATTCATATGGAAGTCCCGGGTCTGTCTTCTTATCA  
TCGGGGTGGCAGCTGGTTCTCAATGTGCCAGCAGGGACTCAGTACCTGAGCCTCAATCAAGC  
CTTATCCACCAAATACACAGGGAAGGGTGATGCAGGGAAGGGTGACATCAGGAGTCAGGGCA  
TGGACTGGTAAGATGAATACTTTGCTGGGCTGAAGCAGGCTGCAGGGCATTCCAGCCAAGGG  
CACAGCAGGGGACAGTGCAGGGAGGTGTGGGGTAAGGGAGGGAAGTCACATCAGAAAAGGGA  
AAGCCACGGAATGTGTGTGAAGCCCAGAAATGGCATTTGCAGTTAATTAGCACATGTGAGGG  
TTAGACAGGTAGGTGAATGCAAGCTCAAGGTTTGGAAAAATGACTTTTCAGTTATGTCTTTG  
GTATCAGACATACGAAAGGTCTCTTTGTAGTTTCGTGTTAATGTAACATTAATAAATTTATG  
ATTCCATTGCTTTAAAAA

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**FIGURE 64**

MWLPLVLLLVAVLLLVAVLCKVYLGLFSGSSPNPFSEDVKRPPAPLVTDKEARKKVLKQAFSAN  
QVPEKLDVVVIGSGFGGLAAAAILAKAGKRVLVLEQHTKAGGCCHTFGKNGLEFDTGIHYIG  
RMEEGSIGRFILDQITEGQLDWAPLSSPFDIMVLEGPNGRKEYPMYSGEKAYIQGLKEKFPQ  
EEAIIIDKYIKLVKVSSGAPHAILLKFLPLPVVQLLDRCGLLTRFSPFLQASTQSLAEVLQQ  
LGASSELQAVLSYIFPTYGVTPNHSAFSMHALLVNHMKGGFYPRGGSSEIAFHTIPVIQRA  
GGAVLTKATVQSVLLDSAGKACGVSVKKGHELVNIYCPIVVSNAGLFNTYEHLLPGNARCLP  
GVKQQLGTVRPGLGMTSVFICLRGTKEDLHLPSTNYYVYYDTMDQAMERYVSMPREEAAEH  
IPLLFFAFPSAKDPTWEDRFPGRSTMIMLIPTAYEWFEEWQAELKGKRGSDYETFKNSFVEA  
SMSVVLKLFPPQLEGKVESVTAGSPLTNQFYLAAPRGACYGADHDLGRLHPCVMASLRAQSPI  
PNLYLTGQDIFTCGLVGALQGALLCSSAILKRNLVSDLKNLDSRIRAQKKKN

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**FIGURE 65**

GCAGCGGCGAGGCGGCGGTGGTGGCTGAGTCCGTGGTGGCAGAGGCGAAGGCGACAGCTCTA  
GGGGTTGGCACCGGCCCGAGAGGAGGATGCGGGTCCGGATAGGGCTGACGCTGCTGCTGTG  
TGCGGTGCTGCTGAGCTTGGCCTCGGCGTCCTCGGATGAAGAAGGCAGCCAGGATGAATCCT  
TAGATTCCAAGACTACTTTGACATCAGATGAGTCAGTAAAGGACCATACTACTGCAGGCAGA  
GTAGTTGCTGGTCAAATATTTCTTGATTGAGAAGAATCTGAATTAGAATCCTCTATTCAAGA  
AGAGGAAGACAGCCTCAAGAGCCAAGAGGGGGAAAGTGTACAGAAGATATCAGCTTTCTAG  
AGTCTCCAAATCCAGAAAACAAGGACTATGAAGAGCCAAAGAAAGTACGGAAACCAGCTTTG  
ACCGCCATTGAAGGCACAGCACATGGGGAGCCCTGCCACTTCCCTTTTCTTTTCTTAGATAA  
GGAGTATGATGAATGTACATCAGATGGGAGGGAAGATGGCAGACTGTGGTGTGCTACAACCT  
ATGACTACAAAGCAGATGAAAAGTGGGGCTTTTGTGAACTGAAGAAGAGGCTGCTAAGAGA  
CGGCAGATGCAGGAAGCAGAAATGATGTATCAAACCTGGAATGAAAATCCTTAATGGAAGCAA  
TAAGAAAAGCCAAAAAAGAGAAGCATATCGGTATCTCCAAAAGGCAGCAAGCATGAACCATA  
CCAAAGCCCTGGAGAGAGTGTGTCATATGCTCTTTTATTTGGTGATTACTTGCCACAGAATATC  
CAGGCAGCGAGAGAGATGTTTGAGAAGCTGACTGAGGAAGGCTCTCCCAAGGGACAGACTGC  
TCTTGGCTTTCTGTATGCCTCTGGACTTGGTGTTAATTCAAGTCAGGCAAAGGCTCTTGAT  
ATTATACATTTGGAGCTCTTGGGGGCAATCTAATAGCCCACATGGTTTTGGTAAGTAGACTT  
TAGTGGAAGGCTAATAATATTAACATCAGAAGAATTTGTGGTTTATAGCGGCCACAACCTTT  
TCAGCTTTCATGATCCAGATTTGCTTGTATTAAGACCAAATATTCAGTTGAACTTCCTTCAA  
ATTCTTGTTAATGGATATAACACATGGAATCTACATGTAAATGAAAGTTGGTGGAGTCCACA  
ATTTTCTTTAAAATGATTAGTTTGGCTGATTGCCCCTAAAAAGAGAGATCTGATAAATGGC  
TCTTTTAAATTTTCTCTGAGTTGGAATTGTCAGAATCATTTTTTACATTAGATTATCATAA  
TTTTAAAATTTTCTTTAGTTTTTCAAATTTTGTAATGGTGGCTATAGAAAAACAACAT  
GAAATATTATACAATATTTTGCAACAATGCCCTAAGAATTGTTAAAATTCATGGAGTTATTT  
GTGCAGAATGACTCCAGAGAGCTCTACTTTCTGTTTTTTACTTTTCATGATTGGCTGTCTTC  
CCATTTATTCTGGTCATTTATTGCTAGTGACACTGTGCCTGCTTCCAGTAGTCTCATTTTCC  
CTATTTTGCTAATTTGTTACTTTTTCTTTGCTAATTTGGAAGATTAACCTCATTTTAAATAAA  
ATTATGTCTAAGATTAAAAA  
AAAAA

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**FIGURE 66**

MRVRIGLTLLLCVLLSLASASSDEEGSQDES LDSKTTLTSDSVKDHTTAGRVVAGQIFLD  
SESELESSIQEEEDSLKSQEGESVTEDISFLESPNPENKDYEEPKKVRKPALTAIEGTAHG  
EPCHFPFLFLDKEYDECTSDGREDGRLWCATTYDYKADEKWGFCETEEEEAAKRRQMQEAEEM  
YQTGMKILNGSNKKSQKREAYRYLQKAASMNHTKALERSYALLFGDYLPQNIQAAREMF EK  
LTEEGSPKGQTALGFLYASGLGVNSSQAKALVYYTFGALGGNLI AHMVLVSRL



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**FIGURE 67**

CTTCCCAGCCCTGTGCCCCAAAGCACCTGGAGCATATAGCCTTGCAGAACTTCTACTTGCCT  
GCCTCCCTGCCTCTGGCCATGGCCTGCCGGTGCCTCAGCTTCCTTCTGATGGGGACCTTCCT  
GTCAGTTTCCCAGACAGTCCTGGCCCAGCTGGATGCACTGCTGGTCTTCCCAGGCCAAGTGG  
CTCAACTCTCCTGCACGCTCAGCCCCCAGCACGTCACCATCAGGGACTACGGTGTGTCCTGG  
TACCAGCAGCGGGCAGGCAGTGCCCCCTCGATATCTCCTCTACTACCGCTCGGAGGAGGATCA  
CCACCGGCCTGCTGACATCCCCGATCGATTCTCGGCAGCCAAGGATGAGGCCCAACAATGCCT  
GTGTCCTCACCATTAGTCCCGTGCAGCCTGAAGACGACGCGGATTACTACTGCTCTGTTGGC  
TACGGCTTTAGTCCCTTAGGGGTGGGGTGTGAGATGGGTGCCTCCCCTCTGCCTCCCATTTCT  
GCCCCTGACCTTGGGTCCCTTTTAACTTTCTCTGAGCCTTGCTTCCCCTCTGTAAAATGGG  
TTAATAATATTCAACATGTCAACAAC

**FIGURE 68**

MACRCLSFLLMGTFLSVSQTVLAQLDALLVFPGQVAQLSCTLSPQHVTIRDYGVSWYQQRAG  
SAPRYLLYYRSEEDHHRPADIPDRFSAKDEAHNACVLTISPVPEDDADYYCSVGYGFSP.

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**FIGURE 69**

GCCGCCCCGCCCCGAGACCGGGCCCCGGGGCGCGGGGCGGCGGGGATGCGGCGCCCCGGGGCGG  
CGATGACCGCGGAGCGCACGCGCGGGCCCCGGCCCTGACCCCGCCGCCCCGCTGAGCCC  
CCCGCCGAGGTCCGGACAGGCCGAGATGACGCGGAGCCCCCTGTTGCTGCTCCTGCTGCCGC  
CGCTGCTGCTGGGGGCCTTCCCACCGGGCCGCGCCGCCCCGAGGCCCCCAAAGATGGCGGAC  
AAGGTGGTCCACGGCAGGTGGCCCCGGCTGGGCGGCACTGTGCGGCTGCAGTGCCAGTGGA  
GGGGGACCCGCGCGCTGACCATGTGGACCAAGGATGGCCGCACCATCCACAGCGGCTGGA  
GCCGCTTCCGCGTGCTGCCGCAGGGGCTGAAGGTGAAGCAGGTGGAGCGGGAGGATGCCGGC  
GTGTACGTGTGCAAGGCCACCAACGGCTTCGGCAGCCTGAGCGTCAACTACACCCTCGTCGT  
GCTGGATGACATTAGCCCAGGGAAGGAGAGCCTGGGGCCCCGACAGCTCCTCTGGGGGTCAAG  
AGGACCCCGCCAGCCAGCAGTGGGCACGACCGCGCTTCACACAGCCCTCCAAGATGAGGCGC  
CGGGTGATCGCACGGCCCCGTGGGTAGCTCCGTGCGGCTCAAGTGCGTGCGCCAGCGGGCACCC  
TCGGCCCCGACATCACGTGGATGAAGGACGACCAGGCCCTTGACGCGCCAGAGGCCGCTGAGC  
CCAGGAAGAAGAAGTGGACACTGAGCCTGAAGAACCTGCGGCCGGAGGACAGCGGCAAATAC  
ACCTGCCGCGTGTCGAACCGCGCGGGCGCCATCAACGCCACCTACAAGGTGGATGTGATCCA  
GCGGACCCGTTCCAAGCCCCGTGCTCACAGGCACGCACCCCGTGAAACACGACGGTGGACTTCG  
GGGGGACCACGTCCTTCCAGTGCAAGGTGCGCAGCGACGTGAAGCCGGTGATCCAGTGGCTG  
AAGCGCGTGGAGTACGGCGCCGAGGGCCGCCACAACCTCCACCATCGATGTGGGCGGCCAGAA  
GTTTGTGGTGCTGCCACGGGTGACGTGTGGTTCGCGGCCCGACGGCTCCTACCTCAATAAGC  
TGCTCATCACCCGTGCCCGCCAGGACGATGCGGGCATGTACATCTGCCTTGGCGCCAACACC  
ATGGGCTACAGCTTCCGCAGCGCCTTCCTCACCGTGCTGCCAGACCCAAAACCGCCAGGGCC  
ACCTGTGGCCTCCTCGTCCTCGGCCACTAGCCTGCCGTGGCCCCGTGGTTCATCGGCATCCAG  
CCGGCGCTGTCTTCATCCTGGGCACCCCTGCTCCTGTGGCTTTGCCAGGCCCCAGAAGAAGCCG  
TGCACCCCCGCGCCTGCCCTCCCCTGCCTGGGCACCGCCCCGCGGGGACGGCCCCGCGACCG  
CAGCGGAGACAAGGACCTTCCCTCGTTGGCCGCCCTCAGCGCTGGCCCTGGTGTGGGGCTGT  
GTGAGGAGCATGGGTCTCCGGCAGCCCCCCCAGCACTTACTGGGCCCAGGCCCAGTTGCTGGC  
CCTAAGTTGTACCCCAAACCTCTACACAGACATCCACACACACACACACACACTCTCACAC  
ACACTCACACGTGGAGGGCAAGGTCCACCAGCACATCCACTATCAGTGCTAGACGGCACCGT  
ATCTGCAGTGGGCACGGGGGGGGCCGGCCAGACAGGCAGACTGGGAGGATGGAGGACGGAGCT  
GCAGACGAAGGCAGGGGACCCATGGCGAGGAGGAATGGCCAGCACCCCAAGGCAGTCTGTGTG  
TGAGGCATAGCCCCCTGGACACACACACACAGACACACACACTACCTGGATGCATGTATGCAC  
ACACATGCGCGCACACGTGCTCCCTGAAGGCACACGTACGCACACGCACATGCACAGATATG  
CCGCTGGGCACACAGATAAGCTGCCCAAATGCACGCACACGCACAGAGACATGCCAGAACA  
TACAAGGACATGCTGCCTGAACATACACACGCACACCCCATGCGCAGATGTGCTGCCTGGACA  
CACACACACACACGGATATGCTGTCTGGACGCACACACGTGCAGATATGGTATCCGGACACA  
CACGTGCACAGATATGCTGCCTGGACACACAGATAATGCTGCCTTGACACACACATGCACGG  
ATATTGCCTGGACACACACACACACACACGCGTGACAGATATGCTGTCTGGACACGCACAC  
ACATGCAGATATGCTGCCTGGACACACACTTCCAGACACACGTGCACAGGCGCAGATATGCT  
GCCTGGACACACGCAGATATGCTGTCTAGTCACACACACACGCAGACATGCTGTCCGGACAC  
ACACACGCATGCACAGATATGCTGTCCGGACACACACACGCACGCAGATATGCTGCCTGGAC  
ACACACACAGATAATGCTGCCTCAACACTCACACACGTGCAGATATTGCCTGGACACACACA  
TGTGCACAGATATGCTGTCTGGACATGCACACACGTGCAGATATGCTGTCCGGATACACACG  
CACGCACACATGCAGATATGCTGCCTGGGCACACACTTCCGGACACACATGCACACACAGGT  
GCAGATATGCTGCCTGGACACACACACAGATAATGCTGCCTCAACACTCACACACGTGCAGA  
TATTGCCTGGACACACACATGTGCACAGATATGCTGTCTGGACATGCACACACGTGCAGATA  
TGCTGTCCGGATACACACGCACGCACACATGCAGATATGCTGCCTGGGCACACACTTCCGGA  
CACACATGCACACACAGGTGCAGATATGCTGCCTGGACACACGCAGACTGACGTGCTTTTGG  
GAGGGTGTGCCGTGAAGCCTGCAGTACGTGTGCCGTGAGGCTCATAGTTGATGAGGGACTTT  
CCCTGCTCCACCGTCACTCCCCAACTCTGCCCGCCTCTGTCCCCGCCTCAGTCCCCGCCTC  
CATCCCCGCCTCTGTCCCCTGGCCTTGGCGGCTATTTTTGCCACCTGCCTTGGGTGCCCAAG  
AGTCCCTACTGCTGTGGGCTGGGGTTGGGGGCACAGCAGCCCCAAGCCTGAGAGGCTGGAG  
CCCATGGCTAGTGGCTCATCCCCAGTGCAATTCTCCCCCTGACACAGAGAAGGGGCCTTGGTA  
TTTATATTTAAGAAATGAAGATAATATTAATAATGATGGAAGGAAGACTGGGTTCAGGGGAC  
TGTGGTCTCTCCTGGGGCCCCGGGACCCGCCTGGTCTTTTCAGCCATGCTGATGACCACACCCC  
GTCCAGGCCAGACACCACCCCCCACTGTCGTGGTGGCCCCAGATCTCTGTAATTTTA  
TGTAGAGTTTGAGCTGAAGCCCCGTATATTTAATTTATTTTGTAAACACAAAA

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**FIGURE 70**

MTPSPLLLLLLPPLLLGAFPPAAAARGPPKMADKVVPRQVARLGRTVRLQCPVEGDPPPLTM  
WTKDGRTIHSGWSRFRVLPQGLKVKQVEREDAGVYVCKATNGFGSLSVNYTLVVLDLDDISPGK  
ESLGPDSSSSGGQEDPASQQWARPRFTQPSKMRRRVVIARPVGSSVRLKCVASGHPRPDITWMK  
DDQALTRPEAAEPRKKKWTLSLKNLRPEDSGKYTCRVSNRAGAINATYKVDVIQRTSRKPVL  
TGTHPVNTTVDFGGTTSFQCKVRSDVKPVIQWLKRVEYGAEGRHNSTIDVGGQKFVVLPTGD  
VWSRPDGSYLNKLLITRARQDDAGMYICLGANTMGYSFRSAFLTVLPDPKPPGPPVASSSSA  
TSLPWPVVIGIPAGAVFILGTLLLWLCQAQKKPCTPAPAPPLPGHRPPGTARDRSGDKDLPS  
LAALSAGPGVGLCEEHGSPAAPQHLLGPGPVAGPKLYPKLYTDIHTHTHTSHHTSHHVEGKV  
HQHIHYQC



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**FIGURE 71A**

CCCAGCTGAGGAGCCCTGCTCAAGACACGGTCACTGGATCTGAGAACTTCCCAGGGGACCG  
CATTCCAGAGTCAGTGACTCTGTGAAGCACCCACATCTACCTCTTGCCACGTTCCCACGGGC  
TTGGGGGAAAGATGGTGGGGACCAAGGCCTGGGTGTTCTCCTTCTTGGTCTTGGGAAGTCACA  
TCTGTGTTGGGGAGACAGACGATGCTCACCCAGTCAGTAAGAAGAGTCCAGCCTGGGAAGAA  
GAACCCAGCATCTTTGCCAAGCCTGCCGACACCCTGGAGAGCCCTGGTGAGTGGACAACAT  
GGTTCAACATCGACTACCCAGGCGGGAAGGGCGACTATGAGCGGCTGGACGCCATTTCGCTTC  
TACTATGGGGACCGTGTATGTGCCCCGTCCCCTGCGGCTAGAGGCTCGGACCACTGACTGGAC  
ACCTGCGGGCAGCACTGGCCAGGTGGTCCATGGTAGTCCCCGTGAGGGTTTCTGGTGCCCTCA  
ACAGGGAGCAGCGGCCTGGCCAGAACTGCTCTAATTACACCGTACGCTTCCTCTGCCCACCA  
GGATCCCTGCGCCGAGACACAGAGCGCATCTGGAGCCCATGGTCTCCCTGGAGCAAGTGCTC  
AGCTGCCTGTGGTCAGACTGGGGTCCAGACTCGCACACGCATTTGCTTGGCAGAGATGGTGT  
CGCTGTGCAGTGAGGCCAGCGAAGAGGGTCACTGTCATGGGCCAGGACTGTACAGCCTGT  
GACCTGACCTGCCCAATGGGCCAGGTGAATGCTGACTGTGATGCCTGCATGTGCCAGGACTT  
CATGCTTCATGGGGCTGTCTCCCTTCCCAGGAGGTGCCCCAGCCTCAGGGGCTGCTATCTACC  
TCCTGACCAAGACGCCGAAGCTGCTGACCCAGACAGACAGTGATGGGAGATTCCGAATCCCT  
GGCTTGTGCCCTGATGGCAAAGCATCCTGAAGATCACAAAGGTCAAGTTTGCCCCCATTGT  
ACTCACAATGCCCAAGACTAGCCTGAAGGCAGCCACCATCAAGGCAGAGTTTGTGAGGGCAG  
AGACTCCATACATGGTGATGAACCTGAGACAAAAGCACGGAGAGCTGGGCAGAGCGTGTCT  
CTGTGCTGTAAGGCCACAGGGAAGCCCAGGCCAGACAAGTATTTTTTGGTATCATAATGACAC  
ATTGCTGGATCCTTCCCTCTACAAGCATGAGAGCAAGCTGGTGCTGAGGAACTGCAGCAGC  
ACCAGGCTGGGGAGTACTTTTGCAAGGCCAGAGTGATGCTGGGGCTGTGAAGTCCAAGGTT  
GCCAGCTGATTGTACAGCATCTGATGAGACTCCTTGCAACCCAGTTCCTGAGAGCTATCT  
TATCCGGCTGCCCCATGATTGCTTTCAGAATGCCACCAACTCCTTCTACTATGACGTGGGAC  
GCTGCCCTGTTAAGACTTGTGCAGGGCAGCAGGATAATGGGATCAGGTGCCGTGATGCTGTG  
CAGAACTGCTGTGGCATCTCCAAGACAGAGGAAAGGGAGATCCAGTGCAGTGGCTACACGCT  
ACCCACCAAGGTGGCCAAGGAGTGACAGCTGCCAGCGGTGTACGGAACTCGGAGCATCGTGC  
GGGGCCGTGTGAGTGCTGCTGACAATGGGGAGCCCATGCGCTTTGGCCATGTGTACATGGGG  
AACAGCCGTGTAAGCATGACTGGCTACAAGGGCACTTTCACCCTCCATGTCCCCCAGGACAC  
TGAGAGGCTGGTGCTCACATTTGTGGACAGGCTGCAGAAGTTTGTCAACACCACCAAAGTGC  
TACCTTTCAACAAGAAGGGGAGTGCCGTGTTCCATGAAATCAAGATGCTTCGTCGGAAAGAG  
CCCATCACTTTGGAAGCCATGGAGACCAACATCATCCCCCTGGGGGAAGTGGTTGGTGAAGA  
CCCCATGGCTGAACTGGAGATTCCATCCAGGAGTTTCTACAGGCAGAATGGGGAGCCCTACA  
TAGGAAAAGTGAAGGCCAGTGTGACCTTCCTGGATCCCCGGAATATTTCCACAGCCACAGCT  
GCCAGACTGACCTGAACTTCATCAATGACGAAGGAGACACTTTCACCCTTCGGACGTATGG  
CATGTTCTCTGTGGACTTCAGAGATGAGGTACCTCAGAGCCACTTAATGCTGGCAAAGTGA  
AGGTCCACCTTGACTCGACCCAGGTCAAGATGCCAGAGCACATATCCACAGTGAAACTCTGG  
TCACTCAATCCAGACACAGGGCTGTGGGAGGAGGAAGGTGATTTCAAATTTGAAAATCAAAG  
GAGGAACAAAAGAGAAGACAGAACCTTCCTGGTGGGCAACCTGGAGATTCGTGAGAGGAGGC  
TCTTTAACCTGGATGTTCTGAAAGCAGGCGGTGCTTTGTTAAGGTGAGGGCCTACCGGAGT  
GAGAGGTTCTTGCCTAGTGAGCAGATCCAGGGGGTGTGTATCTCCGTGATTAACCTGGAGCC  
TAGAACTGGCTTCTTGTTCCAACCCTAGGGCCTGGGGCCGCTTTGACAGTGTCTACAGGCC  
CCAACGGGGCCTGTGTGCCTGCCTTCTGTGATGACCAGTCCCCTGATGCCTACTCTGCCTAT  
GTCTTGGCAAGCCTGGCTGGGGAGGAACTGCAAGCAGTGGAGTCTTCTCCTAAATTCAACCC  
AAATGCAATTGGCGTCCCTCAGCCCTATCTCAACAAGCTCAACTACCGTCGGACGGACCATG  
AGGATCCACGGGTAAAAAGACAGCTTTCCAGATTAGCATGGCCAAGCCAAGGCCCAACTCA  
GCTGAGGAGAGCAATGGGCCCATCTATGCCTTTGAGAACCTCCGGGCATGTGAAGAGGCACC  
ACCCAGTGACGCCACTTCCGGTTCTACCAGATTGAGGGGGATCGATATGACTACAACACAG  
TCCCCTTCAACGAAGATGACCCTATGAGCTGGACTGAAGACTATCTGGCATGGTGGCCAAAG  
CCGATGGAATTCAGGGCCTGCTATATCAAGGTGAAGATTGTGGGGCCACTGGAAGTGAATGT  
GCGATCCCGCAACATGGGGGGCACTCATCGGCGGACAGTGGGGAAGCTGTATGGAATCCGAG  
ATGTGAGGAGCACTCGGGACAGGGACCAAGTGTCTCAGCTGCCTGTCTGGAGTTCAAG  
TGCAGTGGGATGCTCTATGATCAGGACCGTGTGGACCGCACCCCTGGTGAAGGTCAATCCCCA  
GGGCAGCTGCCGTGAGCCAGTGTGAACCCCATGCTGCATGAGTACCTGGTCAACCACTTGC  
CACTTGCAGTCAACAACGACACCAGTGAGTACACCATGCTGGCACCCCTTGGACCCACTGGGC  
CACAACATATGGCATCTACACTGTCACTGACCAGGACCCTCGCACGGCCAAGGAGATCGCGCT  
CGGCCGGTGCTTTGATGGCACATCCGATGGCTCCTCCAGAATCATGAAGAGCAATGTGGGAG  
TAGCCCTCACCTTCAACTGTGTAGAGAGGCAAGTAGGCCGCCAGAGTGCCTTCCAGTACCTC  
CAAAGCACCCAGCCAGTCCCCTGCTGCAGGCACTGTCCAAGGAAGAGTGGCCTCGAGGAG  
GCAGCAGCGAGCGAGCAGGGGTGGCCAGCGCCAGGGTGGAGTGGTGGCCTCTCTGAGATTTC

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**FIGURE 71B**

CTAGAGTTGCTCAACAGCCCCCTGATCAACTAAGTTTTGTGGTACTTCACCCTCTTCTGCCCT  
CATTTTCATGTGACAGCCATTGTGAGACTGATGCACAACTGTCACTTGGTTAATTTAAGCAC  
TTCTGTTTTTCGTGAATTTGCTTGTTTGTTTCTTCATGCCTTTACTTACTTTGTCCCATGCTA  
CTGATTGGCACGTGGCCCCCACAATGGCACAATAAAGCCCCCTTTGTGAACTGTTCTTTAAA  
TGAAACACAAGAAATTGGCCACTGGTAAACTCTGCAGCTTCAACTGTACTTCATTTAATGC  
CATTAATGCAAATATACTTCCTCTTCTTTTTTGCATGGTTTTTGCCACCTCTGCAATAGTGAT  
AATCTGATGCTGAAGATCAAATAACCAATATAAAGCATATTTCTTGGCCTTGCTCCACAGGA  
CATAGGCAAGCCTTGATCATAGTTCATACATATAAATGGTGGTGAAATAAAGAAATAAAACA  
CAATACTTTTACTTGAAATGTAAATAACTTATTTATTTCTTTGCTAAATTTGGAATTCTAGT  
GCACATTCAAAGTTAAGCTATTAAATATAGGGTGATCATAGTTCCTCTACCAAGTCTGGAAA  
GAACATCTCCTGGTATCCACAATTACACCAGGTTGCTAACTGTATTTGTACATTTCCCTTTG  
CATTCGCTTTTGTTCCTTGCTAGAAACCCAGTGTAGCCCAGGGCAGATGTCAATAAATGCATA  
CTCTGTATTTTCGAAAAAA

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**FIGURE 72**

MVGTKAWVFSFLVLEVTSVLGRQTMLTQSVRRVQPGKKNPSIFAKPADTLESPGEWTTWFNI  
DYPGGKGDYERLDAIRFYYGDRVCARPLRLEARTTDWTPAGSTGQVVHGSPREGFWCLNREQ  
RPGQNCSNYTVRFLCPPGSLRRDTERIWSPWSPWSKCSAACGQTGVQTRTRICLAEMVSLCS  
EASEEGQHCMGQDCTACDLTCPMGQVNADCDACMCQDFMLHGAVSLPGGAPASGAAYLLTK  
TPKLLTQTDS DGRFRI PGLCPDGKSILKITKVKFAPIVLTMPKTS LKAATIKAEFVRAETPY  
MVMNPETKARRAGQSVSLCCKATGKPRPDKYFWYHNDTLLDPSLYKHESKLVLRLKLOQHQAQ  
EYFCKAQSDAGAVKSKVAQLIVTASDETPCNPVPESYLIRLPHDCFQ NATNSFY YDVGRCPV  
KTCAGQQDNGIRCRDAVQNCCGISKTEEREIQCSGYTLPTKVAKECSCQRCTETRSIVRGRV  
SAADNGEPMRFGHVYMGNSRVSM TGYKGTFTLHVPQDTERLVLT FVDRLQKFVNTTKVLPFN  
KKGSAVFHEIKMLRRKEPITLEAMETNIIPLGEVVGEDPMAELEIPSR SFYRQNGEPYIGKV  
KASVTFLDPRNISTATAAQTDLNFINDEGDTFPLRTYGMFSVDFRDEVTSEPLNAGKVKVHL  
DSTQVKMPEHISTVKLWSLNPDTGLWEEEGDFKFENQRRNKREDRTFLVGNLEIRERRLFNL  
DVPESRRCFVKVRAYRSERFLPSEQIQGVVISVINLEPRTGFLSNPRAWGRFDSVITGPNGA  
CVPAFCDDQSPDAYSAYVLASLAGEELQAVESSPKFNPNAIGVPQPYLNKLN YRRTDHEDPR  
VKKTAFQISMAKPRPNSAEESNGPIYAFENLRACEEAPPSAAHFRFYQIEGDRYDYNTVPFN  
EDDPMSWTEDYLAWWPKPMEFRACYIKVKIVGPLEVNVR SRNMGGTHRRTVGKLYGIRDVRS  
TRDRDQPNVSAACLEFKCSGMLYDQDRVDRTL VKVIPQGSCRRASVNPMLHEYLVNHLPLAV  
NNDTSEYTMLAPLDPLGHNYGIYTVTDQDPRTAKEIALGRCFDGTSDGSSRIMKSNVGVALT  
FNCVERQVGRQSAFQYLQSTPAQSPAAGTVQGRVPSRRQQRASRGGQRQGGVVASLRFP RVA  
QQPLIN

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**FIGURE 73**

CTGCAAGTTGTTAACGCCTAACACACAAGTATGTTAGGCTTCCACCAAAGTCCTCAATATAC  
CTGAATACGCACAATATCTTAACCTCTTCATATTTGGTTTTGGGATCTGCTTTGAGGTCCCAT  
CTTCATTTAAAAAAAATACAGAGACCTACCTACCCGTACGCATACATATGTGTATAT  
ATATGTAAACTAGACAAAGATCGCAGATCATAAAGCAAGCTCTGCTTTAGTTTCCAAGAAGA  
TTACAAAGAATTTAGAGATGTATTTGTCAAGATCCCTGTGATTTCATGCCCTTTGGGTACG  
GTGTCCTCAGTGATGCAGCCCTACCCTTTGGTTTGGGGACATTATGATTTGTGTAAGACTCA  
GATTTACACGGAAGAAGGGAAAGTTTGGGATTACATGGCCTGCCAGCCGGAATCCACGGACA  
TGACAAAATATCTGAAAGTGAACTCGATCCTCCGGATATTACCTGTGGAGACCCTCCTGAG  
ACGTTCTGTGCAATGGGCAATCCCTACATGTGCAATAATGAGTGTGATGCGAGTACCCTGA  
GCTGGCACACCCCCCTGAGCTGATGTTTGATTTTGAAGGAAGACATCCCTCCACATTTTGGC  
AGTCTGCCACTTGGAAGGAGTATCCCAAGCCTCTCCAGGTAAACATCACTCTGTCTTGAGC  
AAAACCATTGAGCTAACAGACAACATAGTTATTACCTTTGAATCTGGGCGTCCAGACCAAAT  
GATCCTGGAGAAGTCTCTCGATTATGGACGAACATGGCAGCCCTATCAGTATTATGCCACAG  
ACTGCTTAGATGCTTTTTCACATGGATCCTAAATCCGTGAAGGATTTATCACAGCATACGGTC  
TTAGAAATCATTTGCACAGAAGAGTACTCAACAGGGTATAACAATAAGCAAAATAATCCA  
CTTTGAAATCAAAGACAGGTTTCGCGCTTTTGTGCTGGACCTCGCCTACGCAATATGGCTTCCC  
TCTACGGACAGCTGGATACAACCAAGAACTCAGAGATTTCTTTACAGTCACAGACCTGAGG  
ATAAGGCTGTTAAGACCAGCCGTTGGGGAAATATTTGTAGATGAGCTACACTTGGCACGCTA  
CTTTTACGCGATCTCAGACATAAAGGTGCGAGGAAGGTGCAAGTGTAATCTCCATGCCACTG  
TATGTGTGTATGACAACAGCAAATTGACATGCGAATGTGAGCACAACACTACAGGTCCAGAC  
TGTGGGAAATGCAAGAAGAATTATCAGGGCCGACCTTGGAGTCCAGGCTCCTATCTCCCCAT  
CCCCAAAGGCACTGCAATACCTGTATCCCCAGTATTTCCAGTATTGGTACGAATGTCTGCG  
ACAACGAGCTCCTGCACTGCCAGAACGGAGGGACGTGCCACAACAACGTGCGCTGCCTGTGC  
CCGGCCGCATACACGGGCATCCTCTGCGAGAAGCTGCGGTGCGAGGAGGCTGGCAGCTGCGG  
CTCCGACTCTGGCCAGGGCGCGCCCCCGCACGGCACCCCAGCGCTGCTGCTGCTGACCACGC  
TGCTGGGAACCGCCAGCCCCCTGGTGTTCTAGGTGTACCTCCAGCCACACCGGACGGGCCT  
GTGCCGTGGGGAAGCAGACACAACCCAAACATTTGCTACTAACATAGGAAACACACACATAC  
AGACACCCCCACTCAGACAGTGTACAACTAAGAAGGCCTAACTGAACTAAGCCATATTTAT  
CACCCGTGGACAGCACATCCGAGTCAAGACTGTAAATTTCTGACTCCAGAGGAGTTGGCAGC  
TGTTGATATTATCACTGCAATCACATTGCCAGCTGCAGAGCATATTGTGGATTGGAAAGGC  
TGCGACAGCCCCCAAACAGGAAAGACAAAAACAAACAATCAACCGACCTAAAAACATTG  
GCTACTCTAGCGTGGTGCGCCCTAGTACGACTCCGCCCAGTGTGTGGACCAACCAATAGCA  
TTCTTTGCTGTCAGGTGCATTGTGGGCATAAGGAAATCTGTTACAAGCTGCCATATTGGCCT  
GCTTCCGTCCCTGAATCCCTTCCAACCTGTGCTTTAGTGAACGTTGCTCTGTAACCCCTCGTT  
GGTTGAAAGATTTCTTTGTCTGATGTTAGTGATGCACATGTGTAACAGCCCCCTCTAAAAGC  
GCAAGCCAGTCATACCCCTGTATATCTTAGCAGCACTGAGTCCAGTGCGAGCACACACCCAC  
TATACAAGAGTGGCTATAGGAAAAAAGAAAGTGTATCTATCCTTTTGTATTCAAATGAAGTT  
ATTTTTCTTGAACACTGTAAATATGTAGATTTTTTTGTATTATTGCCAATTTGTGTTACCAGA  
CAATCTGTTAATGTATCTAATTCGAATCAGCAAAGACTGACATTTTATTTTGTCTCTTTTCG  
TTCTGTTTTGTTTCACTGTGCAGAGATTTCTCTGTAAAGGCAACGAACGTGCTGGCATCAAA  
GAATATCAGTTTACATATATAACAAGTGTAATAAGATTCCACCAAAGGACATTCTAAATGTT  
TTCTTGTTGCTTTAACACTGGAAGATTTAAAGAATAAAAACCTCCTGCATAAACGATTTTCAGG  
AATTTGTATTGCAATTTCTTAAGATGAAAGGAACAGCCACCAAGCAGTTTCACACTCACTTT  
ACTGATTTCTGTGTGGACTGAGTACATTGAGCTGACGAATTTAGTTCCCAGGAAGATGGATT  
GATGTTCACTAGCTTGGACAACCTTCTGCAAAATATGAGACTATTTCCACTTGGGAAAAATTA  
CAACAGCAAAAAAAAAAAAAAAAAAAAAA



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**FIGURE 74**

MYLSRSLSIHALWVTVSSVMQPYPLVWGHYDLCKTQIYTEEGKVWDYMACQPESTDMTKYLK  
VKLDPPDITCGDPPETFCAMGNPYMCNNECDASTPELAHPPELMFDFEGRHPSTFWQSATWK  
EYPKPLQVNITLSWSKTIELTDNIVITFESGRPDQMILEKSLDYGRTWQPYQYYATDCLDAF  
HMDPKSVKDLSQHTVLEIICTEEYSTGYTTNSKIIHFEIKDRFALFAGPRLRNMASLYGQLD  
TTKKLRDFFTVDLRIRLLRPAVGEIFVDELHLARYFYAISDIKVRGRCKCNLHATVCVYDN  
SKLTCECEHNTTGPDCGKCKKNYQGRPWSPGSYLPIPKGTANTCIPSISSIGTNVCDNELLH  
CQNGGTCHNNVRCLCPAAYTGILCEKLRCEEAGSCGSDSGQGAPPHGTPALLLLTTLLGTAS  
PLVF

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**FIGURE 75**

CCCACGCGTCCGGGTGACCTGGGCCGAGCCCTCCCGGTCCGGCTAAGATTGCTGAGGAGGCGG  
CGGGTAGCTGGCAGGCGCCGACTTCCGAAGGCCGCCGTCCGGGCGAGGTGTCCTCATGACTT  
CTCTTGTGGACCAATGTCCGTGATCTTTTTTGCCTGCGTGGTACGGGTAAGGGATGGACTGCC  
CCTCTCAGCCTCTACTGATTTTTTACCACACCCAAGATTTTTTGGAAATGGAGGAGACGGCTCA  
AGAGTTTAGCCTTGCGACTGGCCCAGTATCCAGGTCGAGGTTCTGCAGAAGGTTGTGACTTT  
AGTATACATTTTTTCTTCTTTCGGGGACGTGGCCTGCATGGCTATCTGCTCCTGCCAGTGTCC  
AGCAGCCATGGCCTTCTGCTTCCTGGAGACCCTGTGGTGGGAATTCACAGCTTCCTATGACA  
CTACCTGCATTGGCCTAGCCTCCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTCAG  
AAAGTGAAGTGGCATTTTAACTATGTAAGTTCCTCTCAGATGGAGTGCAGCTTGAAAAAAT  
TCAGGAGGAGCTCAAGTTGCAGCCTCCAGCGGTTCTCACTCTGGAGGACACAGATGTGGCAA  
ATGGGGTGATGAATGGTCACACACCGATGCACTTGGAGCCTGCTCCTAATTTCCGAATGGAA  
CCAGTGACAGCCCTGGGTATCCTCTCCCTCATTCTCAACATCATGTGTGCTGCCCTGAATCT  
CATTCGAGGAGTTCACCTTGCAGAACATTCTTTACAGGATCCAAGGAGCTGGTTCTGCTGGT  
TGGACCAAACCTCGTGAGCCAGCCACCCCTGACCCAAATGAGGAGAGCTCTGATTCTCCCAT  
CCGGGAGCAGTGATGTCAAACCTTCTGCTGCTGGGGAAATCTCATCAGCAGGGAGCCTGTGGA  
AAAGGGCATGTCAGTGAAATCTGGGAATGGCTGGATTCCGGAACATCTGCCCATGTGTATTG  
ATGGCAGAGCTGTTGCCCACAAGCGCCTTTTATTTAGGGTAAAATTAACAAATCCATTCTAT  
TCCTCTGACCCATGCTTAGTACATATGACCTTTAACCCTTACATTTATATGATTCTGGGGTT  
GCTTCAGAAGTGTTATTTTCATGAATCATTCATATGATTTGATCCCCCAGGATTCTATTTTGT  
TTAATGGGCTTTTCTACTAAAAGCATAAAATACTGAGGCTGATTTAGTCAGGGCAAAACCAT  
TTACTTTACATATTCGTTTTCAATACTTGCTGTTTCATGTTACACAAGCTTCTTACGGTTTTTC  
TTGTAACAATAAATATTTTGAGTAAATAATGGGTACATTTTAACAAACTCAGTAGTACAACC  
TAAACTTGTATAAAAGTGTGTAAAAATGTATAGCCATTTATATCCTATGTATAAATTAAATG  
AGGTGGCTTCAGAAATGGCAGAATAAATCTAAAGTGTTTATTAAAAA  
AAAAG

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**FIGURE 76**

MSVIFFACVVRVRDGLPLSASTDFYHTQDFLEWRRRLKSLALRLAQYPGRGSAEGCDFS IHF  
SSFGDVACMAICSCQCPAAMAFCFLETLWWEFTASYDTTCIGLASRPYAFLEFDSIIQKVKW  
HFNYVSSSQMECSLEKIQEELKLQPPAVLTLEDTDVANGVMNGHTPMHLEPAPNFRMEPVTA  
LGILSLILNIMCAALNLIRGVHLAEHSLQDPRSWFCWLDQTS

**FIGURE 77**

TGCTTCCTGGAGACCCTGTGGTGGGAATTCACAGCTTCNTATGACACTACCTGCATTGGCNT  
AGCCTCCAGGCCATACGCTTTTCTTGAGTTTGACAGCATCATTCAGAAAGTGAAGTGGCATT  
TTAACTATGTAAGTTCCTNTCAGATGGAGTGCAGCTTGGAAAAAATTCAGGAGGAGCTCAAG  
TTGCAGCCTCCAGCGGTTCTCANTATGGAGGACACAGATGTGGCAAATGGGGT



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**FIGURE 78**

CTCAGCGGCGCTTCCTCGTAGCGAGCCTAGTGGCGGGTGTTTGCATTGAAACGTGAGCGCGA  
CCCGACCTTAAAGAGTGGGGAGCAAAGGGAGGACAGAGCCCTTTAAAACGAGGCGGGTGGTG  
CCTGCCCCCTTTAAGGGCGGGGCGTCCGGACGACTGTATCTGAGCCCCAGACTGCCCCGAGTT  
TCTGTGCGCAGGCTGCGAGGAAAGGCCCTAGGCTGGGTCTGGGTGCTTGGCGGCGGCGGCTT  
CCTCCCCGCTCGTCCTCCCCGGGCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTA  
TGGAAGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGC  
GAGTGTATTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTTCCTGAC  
CCGCTTCAAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCGTCAACAAGA  
TTGCGCTCGAGCTGTGCACCTTTACCCTGGCAATTGCCCTGGGTGCTGTCTGCTCCTGCCC  
TTCTCCATCATCAGCAATGAGGTGCTGCTCTCCCTGCCTCGGAACACTACTACATCCAGTGGCT  
CAACGGCTCCCTCATCCATGGCCTCTGGAACCTTGTTTTTCTCTTCCCCAACCTGTCCCTCA  
TCTTCCTCATGCCCTTTGCATATTTCTTCACTGAGTCTGAGGGCTTTGCTGGCTCCAGAAAG  
GGTGTCTGGGCGGGTCTATGAGACAGTGGTGATGTTGATGCTCCTCACTCTGCTGGTGCT  
AGGTATGGTGTGGGTGGCATCAGCCATTGTGGACAAGAACAAGGCCAACAGAGAGTCACTCT  
ATGACTTTTGGGAGTACTATCTCCCCTACCTCTACTCATGCATCTCCTTCCTTGGGGTTCTG  
CTGCTCCTGGTGTGTACTCCACTGGGTCTCGCCCGCATGTTCTCCGTCACTGGGAAGCTGCT  
AGTCAAGCCCCGGCTGCTGGAAGACCTGGAGGAGCAGCTGTACTGCTCAGCCTTTGAGGAGG  
CAGCCCTGACCCGCAGGATCTGTAATCCTACTTCCTGCTGGCTGCCTTTAGACATGGAGCTG  
CTACACAGACAGGTCTGGCTCTGCAGACACAGAGGGTCTGCTGGAGAAGAGGCGGAAGGC  
TTCAGCCTGGCAACGGAACCTGGGCTACCCCCTGGCTATGCTGTGCTTGCTGGTGCTGACGG  
GCCTGTCTGTGCTCATTGTGGCCATCCACATCCTGGAGCTGCTCATCGATGAGGCTGCCATG  
CCCCGAGGCATGCAGGGTACCTCCTTAGGCCAGGTCTCCTTCTCCAAGCTGGGCTCCTTTGG  
TGCCGTCATTCAGGTTGTACTCATCTTTTACCTAATGGTGTCTCAGTTGTGGGCTTCTATA  
GCTCTCCACTCTTCCGGAGCCTGCGGCCAGATGGCACGACACTGCCATGACGCAGATAATT  
GGGAACTGTGTCTGTCTCCTGGTCCTAAGCTCAGCACTTCCTGTCTTCTCTCGAACCTGGG  
GCTCACTCGCTTTGACCTGCTGGGTGACTTTGGACGCTTCAACTGGCTGGGCAATTTCTACA  
TTGTGTTCTCTACAACGCAGCCTTTGCAGGCCTCACCACACTCTGTCTGGTGAAGACCTTC  
ACTGCAGCTGTGCGGGCAGAGCTGATCCGGGCCTTTGGGCTGGACAGACTGCCGCTGCCCGT  
CTCCGGTTTCCCCCAGGCATCTAGGAAGACCCAGCACCAGTGACCTCCAGCTGGGGGTGGGA  
AGGAAAAAACTGGACACTGCCATCTGCTGCCTAGGCCTGGAGGGAAGCCCAAGGCTACTTGG  
ACCTCAGGACCTGGAATCTGAGAGGGTGGGTGGCAGAGGGGAGCAGAGCCATCTGCACTATT  
GCATAATCTGAGCCAGAGTTTGGGACCAGGACCTCCTGCTTTTCCATACTTAACTGTGGCCT  
CAGCATGGGGTAGGGCTGGGTGACTGGGTCTAGCCCCTGATCCCAAATCTGTTTACACATCA  
ATCTGCCTCACTGCTGTTCTGGGCCATCCCCATAGCCATGTTTACATGATTTGATGTGCAAT  
AGGGTGGGGTAGGGGCAGGGAAAGGACTGGGCCAGGGCAGGCTCGGGAGATAGATTGTCTCC  
CTTGCTCTGGCCCAGCAGAGCCTAAGCACTGTGCTATCCTGGAGGGGCTTTGGACCACCTG  
AAAGACCAAGGGGATAGGGAGGAGGAGGCTTCAGCCATCAGCAATAAAGTTGATCCCAGGGA  
AAAAAA

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**FIGURE 79**

MEAPDYEVLSVREQLFHERIRECIISTLLFATLYILCHIFLTRFKKPAEFTTVDDDEDATV NK  
IALELCTFTLAIALGAVLLLPFSIISNEVLLSLPRNYYIQWLNGSLIHGLWNLVFLFPNLSL  
IFLMPFAYFFTESEGFAGSRKGV LGRVYETVVMLMLLTLLVLGMVWVASAIVDKNKANRESL  
YDFWEYYLPYLYSCISFLGVLLLLVCTPLGLARMFSVTGKLLVKPRLLEDLEEQLYCSAFEE  
AALTRRICNPTSCWLPLDMELLHRQVLALQTQRVLLEKRRKASAWQRNLGYPLAMLCLLVLT  
GLSVLIVAIHILELLIDEAAMP RGMQGTSLGQVSFSKLGSGAVIQVVLIFYLMVSSVVG FY  
SSPLFRSLRPRWHD TAMTQIIGNCVCLLVLSALPVFSRTLGLTRFDLLGDFGRFNWLG NFY  
IVFLYNAAFAGLTTLCLVKTF TA AVRAELIRAFGLDRLPLPVSGFPQASRKTQH Q

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**FIGURE 80**

GGCTGCCGAGGGAAGGCCCTTGGGTTGGTCTTGGTTGCTTGGCGGCGGCGGNTTCNTCCCC  
GCTCGTCCTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTATGGAAGC  
ACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGCGAGTGTA  
TTATATCAACACTTCTGTTTGCAACACTGTACATCCTCTGCCACATCTTCCTGACCCGCTTC  
AAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCG

**FIGURE 81**

GACCGACCTTAAAGAGTGGGAGCAAAGGGAGGACAGAGCCTTTTAAAACGAGGCGGTGGTGC  
CTGCCCTTTAAGGGCGGGGCGTCCGGACGACTGTATCTGAGCCCCAGACTGCCCCGAGTTTC  
TGTCGCAGGCTGCGAGGAAAGGCCCTAGGCTGGGTCTGGTGCTTGGCGGCGGCGGCTTCCT  
CCCCGTTGTCNTCCCCGGGCCCAGAGGCACCTCGGCTTCAGTCATGCTGAGCAGAGTATGGA  
AGCACCTGACTACGAAGTGCTATCCGTGCGAGAACAGCTATTCCACGAGAGGATCCGCGAGT  
GTATTATATCAACACTTCTGTTTGCAACACTGTACATCNTCTGCCACATCTTCCTGACCCGC  
TTCAAGAAGCCTGCTGAGTTCACCACAGTGGATGATGAAGATGCCACCGTCAACAAGATTGC  
GCTCGAGCTGTGCACCTTTACCCTGGCAATTGCCCTGGGTGCTGTCCTGCTCCTGCCCTTCT  
CCATCATCAGCAATGAGGTGCTGCACTCCC



**FIGURE 82**

GATGTGCTCCTTGGAGCTGGTGTGCAGTGTCTGACTGTAAGATCAAGTCCAAACCTGTTTT  
GGAATTGAGGAACTTCTCTTTTGATCTCAGCCCTTGGTGGTCCAGGTCTTCATGCTGCTGT  
GGGTGATATTACTGGTCCTGGCTCCTGTCAGTGGACAGTTTGCAAGGACACCCAGGCCCAT  
ATTTTCCTCCAGCCTCCATGGACCACAGTCTTCCAAGGAGAGAGAGTGACCCTCACTTGCAA  
GGGATTTGCTTCTACTCACCACAGAAAACAAAATGGTACCATCGGTACCTTGGGAAAGAAA  
TACTAAGAGAAACCCCAGACAATATCCTTGAGGTTTCAGGAATCTGGAGAGTACAGATGCCAG  
GCCCAGGGCTCCCCTCTCAGTAGCCCTGTGCACTTGGATTTTTCTTCAGAGATGGGATTTCC  
TCATGCTGCCCAGGCTAATGTTGAACTCCTGGGCTCAAGTGATCTGCTCACCTAGGCCTCTC  
AAAGCGCTGGGATTACAGCTTCGCTGATCCTGCAAGCTCCACTTTCTGTGTTTGAAGGAGAC  
TCTGTGGTTCTGAGGTGCCGGGCAAAGGCGGAAGTAACACTGAATAATACTATTTACAAGAA  
TGATAATGTCCTGGCATTCTTAATAAAAGAACTGACTTCCAAAAAAAAAAAAAAAAAAAAA

**FIGURE 83**

MLLVILLVLAPVSGQFARTPRPIIFLQPPWTTVFQGERVTLTCKGFRFYSPQTKWYHRYL  
GKEILRETPDNILEVQESGEYRCQAQGSPLSSPVHLDFSSEMGFPHAAQANVELLGSSDLLT

**FIGURE 84**

CAGAAGAGGGGGCTAGCTAGCTGTCTCTGCGGACCAGGGAGACCCCCGCGCCCCCCCCGGTGT  
GAGGCGGCCTCACAGGGCCGGGTGGGCTGGCGAGCCGACGCGGCGGCGGAGGAGGCTGTGAG  
GAGTGTGTGGAACAGGACCCGGGACAGAGGAACCATGGCTCCGCAGAACCTGAGCACCTTTT  
GCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATAAGATCTTG  
GGGGTGCCCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAACTAGCCCTGCA  
GCTTCATCCCGACCGGAACCCTGATGATCCACAAGCCCAGGAGAAATTCCAGGATCTGGGTG  
CTGCTTATGAGGTTCTGTCAGATAGTGAGAAACGGAAACAGTACGATACTTATGGTGAAGAA  
GGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTTCACACTTCTTTGGGGATTT  
TGGTTTCATGTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATATTCCAAGAGGAAGTGATA  
TTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAGGAAATTTTGTGGAAGTAGTT  
AGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGAAGTGCAATTGTCGGCAAGAGAT  
GCGGACCACCCAGCTGGGCCCTGGGCGCTTCCAAATGACCCAGGAGGTGGTCTGCGACGAAT  
GCCCTAATGTCAAACCTAGTGAATGAAGAACGAACGCTGGAAGTAGAAATAGAGCCTGGGGTG  
AGAGACGGCATGGAGTACCCCTTTATTGGAGAAGGTGAGCCTCACGTGGATGGGGAGCCTGG  
AGATTTACGGTTCCGAATCAAAGTTGTCAAGCACCCAATATTTGAAAGGAGAGGAGATGATT  
TGTACACAAATGTGACAATCTCATTAGTTGAGTCACTGGTTGGCTTTGAGATGGATATTACT  
CACTTGGATGGTCACAAGGTACATATTTCCCGGGATAAGATCACCAGGCCAGGAGCGAAGCT  
ATGGAAGAAAGGGGAAGGGCTCCCCAACTTTGACAACAACAATATCAAGGGCTCTTTGATAA  
TCACTTTTGATGTGGATTTTCCAAAAGAACAGTTAACAGAGGAAGCGAGAGAAGGTATCAAA  
CAGCTACTGAAACAAGGGTCAGTGCAGAAGGTATACAATGGACTGCAAGGATATTGAGAGTG  
AATAAAATTGGACTTTGTTTAAATAAGTGAATAAGCGATATTTATTATCTGCAAGGTTTTT  
TTGTGTGTGTTTTTGTTTTTTATTTTCAATATGCAAGTTAGGCTTAATTTTTTTTATCTAATGA  
TCATCATGAAATGAATAAGAGGGCTTAAGAATTTGTCCATTTGCATTCGGAAAAGAATGACC  
AGCAAAAGGTTTACTAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCCTGAGT  
TTCAAGAATTAAAGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGA  
GTTGTTAGCAATTTCAATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTG  
TTATTTTAA

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**FIGURE 85**

MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRSASIKDIKKAYRKLALQLHPDRNPDDPQ  
AQEKFDLGAAYEVLSDSEKRRQYDTYGEEGLKDGHQSSHGDIFSHFFGDFGFMFGGTTPRQQ  
DRNIPRGSDIIVDLEVTLEEVYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTTQLGPGRFQ  
MTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGMETPFIDGEPEPHVDGEPGDLRFRIKVVKH  
PIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVVHISRDKITRPGAKLWKKGEGLPNFD  
NNNIKGSIIITFDVDFPKEQLTEEAREGIKQLLKQGSVQKVYNGLQGY



**FIGURE 86**

TGGGACCAGGGAACCCCGGGCCCCCGGTGGAGNGCCTAACAGGCCGGTGGNTGCGACCGAA  
GCGGCGGGCGGAGGAGGTTTTGAGGATTTTTGGAACAGGACCCGGACAGAGGAACCATGGTT  
CCGCAGAACNTGAGCACNTTTTGCCTGTTGNTGNTATACTTCATCGGGGCGGTGATTGCCGG  
ACGAGATTTNTATAAGATTTTGGGGTGCCTNGAAGTGCCTTNTATAAAGGATATTA AAAAGG  
CCTATAGGAAACTAGCCCTGCAGNTTATCCCGACCGGAACCCTGATGATCCACAAGCCCAG  
GAGAAATTCCAGGATTTGGGTGCTGCTTATGAGGTTNTGTCAGATAGTGAGAAACGGAAACA  
GTACGATAATTATGGTGAAGAAGGATTAAAAGATGGTNATCAGAGCTCCCATGGAGACATTT  
TTTCACACTTNTTTGGGGATTTTGGTTTCATGTTTGGAGGAACCCCTNGTCAGCAAGACAGA  
AATATTCCAAGAG

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**FIGURE 87**

GGCACGAGGCGGCGGGGCAGTCGCGGGATGCGCCCGGGAGCCACAGCCTGAGGCCCTCAGGT  
CTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTTGCCACTTCCA  
GCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAAGCATGG  
AGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGTTTGCAGCC  
TTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGGCCGCGAGACCTGCTGCAGCGCTATGATTC  
TAAGCCCATTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCTCTGAGTTAGAAC  
TGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGAATGAAGACTGGATC  
GAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGATTTGTCACTCTGAC  
AGAGAAGCTTGTTGCCATGACAATGGGCTCTGGGGCCAAGATGAAGACTTCAGCCAGTGTCA  
GCGACATCATTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGGATGATGTTGTGAAGTCGATG  
TACCCTCCGTTGGACCCCAAACCTCCTGGACGCACGGACGACTGCCCTGCTCCTGTCTGTCAG  
TCACCTGGTGCTGGTGACAAGGAATGCCTGCCATCTGACGGGAGGCCTGGACTGGATTGACC  
AGTCTCTGTCGGCTGCTGAGGAGCATTTGGAAGTCCTTCGAGAAGCAGCCCTAGCTTCTGAG  
CCAGATAAAGGCCTCCCAGGCCCTGAAGGCTTCCTGCAGGAGCAGTCTGCAATTTAGTGCCT  
ACAGGCCAGCAGCTAGCCATGAAGGCCCTGCCGCCATCCCTGGATGGCTCAGCTTAGCCTT  
CTACTTTTTCTATAGAGTTAGTTGTTCTCCACGGCTGGAGAGTTCAGCTGTGTGTGCATAG  
TAAAGCAGGAGATCCCCGTCAGTTTATGCCTCTTTTGCAGTTGCAAACTGTGGCTGGTGAGT  
GGCAGTCTAATACTACAGTTAGGGGAGATGCCATTCACCTCTCTGCAAGAGGAGTATTGAAAA  
CTGGTGGACTGTCAGCTTTATTTAGCTCACCTAGTGTTTTCAAGAAAATTGAGCCACCGTCT  
AAGAAATCAAGAGGTTTCACATTAAAATTAGAATTTCTGGCCTCTCTCGATCGGTCAGAATG  
TGTGGCAATTCTGATCTGCATTTTCAGAAGAGGACAATCAATTGAACTAAGTAGGGGTTTC  
TTCTTTTGGCAAGACTTGTA CTCTCACCTGGCCTGTTTCATTTATTTGTATTATCTGCCT  
GGTCCCTGAGGCGTCTGGGTCTCTCCTCTCCCTTGCAGGTTTGGGTTTGAAGCTGAGGAACT  
ACAAAGTTGATGATTTCTTTTTTATCTTTATGCCTGCAATTTTACCTAGCTACCACTAGGTG  
GATAGTAAATTTATACTTATGTTTCCCTCAAAAAAAAAAAAAAA

**FIGURE 88**

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPSEL  
ELDDVVITNPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMKTSAS  
VSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLSVSHLVLVTRNACHLTGGLDWI  
DQSLSAEEHLEVLREAALASEPDKGLPGPEGFLQEQSAI

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**FIGURE 89**

GCTTCATTTCTCCCGACTCAGCTTCCCACCCTGGGCTTTCCGAGGTGCTTTCGCCGCTGTCC  
CCACCACTGCAGCCATGATCTCCTTAACGGACACGCAGAAAATTGGAATGGGATTAACAGGA  
TTTGGAGTGTTTTTCCTGTTCTTTGGAATGATTCTCTTTTTTGACAAAGCACTACTGGCTAT  
TGGAATGTTTTATTTGTAGCCGGCTTGGCTTTTGTAATTGGTTTAGAAAGAACATTCAGAT  
TCTTCTTCCAAAAACATAAAATGAAAGCTACAGGTTTTTTTTCTGGGTGGTGTATTTGTAGTC  
CTTATTGGTTGGCCTTTGATAGGCATGATCTTCGAAATTTATGGATTTTTTTCTCTTGTTTCAG  
GGGCTTCTTTCCTGTCGTTGTTGGCTTTATTAGAAGAGTGCCAGTCCTTGGATCCCTCCTAAAT  
TTACCTGGAATTAGATCATTTGTAGATAAAGTTGGAGAAAGCAACAATATGGTATACACAACA  
AGTGAATTTGAAGACTCATTTAAAATATTGTGTTATTTATAAAGTCATTTGAAGAATATTCA  
GCACAAAATTAAATTACATGAAATAGCTTGTAATGTTCTTTACAGGAGTTTAAAACGTATAG  
CCTACAAAGTACCAGCAGCAAATTAGCAAAGAAGCAGTGAAAACAGGCTTCTACTCAAGTGA  
ACTAAGAAGAAGTCAGCAAGCAAACCTGAGAGAGGTGAAATCCATGTTAATGATGCTTAAGAA  
ACTCTTGAAGGCTATTTGTGTTGTTTTTCCACAATGTGCGAAACTCAGCCATCCTTAGAGAA  
CTGTGGTGCTGTTTCTTTTCTTTTATTTTGAAGGCTCAGGAGCATCCATAGGCATTTGCT  
TTTTAGAAGTGTCCACTGCAATGGCAAAAATATTTCCAGTTGCACTGTATCTCTGGAAGTGA  
TGCATGAATTCGATTGGATTGTGTCATTTTAAAGTATTAAAACCAAGGAAACCCCAATTTTG  
ATGTATGGATTACTTTTTTTTGNGCNCAGGGCC



**FIGURE 90**

MISLTDQTQKIGMGLTGFGVFFLFFGMILFFDKALLAIGNVLFVAGLAFVIGLERTFRFFFQK  
HKMKATGFFLGGVFVVLIGWPLIGMIFEIYGFFLLFRGFFPVVVGFI RRVPVLGSLLNLPGI  
RSFVDKVGESNNMV

**Important features:**

**Transmembrane domains:**

amino acids 12-30 (typeII), 33-52, 69-89 and 93-109

**N-myristoylation sites.**

amino acids 11-16, 51-56 and 116-121

**Aminoacyl-transfer RNA synthetases class-II protein.**

amino acids 49-59

**FIGURE 91**

GAAGACGTGGCGGCTCTCGCCTGGGCTGTTTCCCGGCTTCATTTCTCCCGACTCAGCTTCCC  
ACCNTGGGCTTTCCGAGGTGCTTTCGCCGCTGTCCCCACCACTGCAGCCATGATCTCCTTAA  
CGGACACGCAGAAAATTGGAATGGGATTAACCGGATTTGGAGTGTTTTCTGTTCTTTGGA  
ATGATTCTCTTTTTTGACAAAGCACTACTGGCTATTGGAAATGTTTTATTTGTAGCCGGCTT  
GGCTTTTGTAATTGGTTTAGAAAGAACATTCAGATTCTTCTTCCAAAACATAAAATGAAAG  
CTACAGGTTTTTTTCTGGGTGGTGTATTTGTAGTCCTTATTGGTTGGCCTTTGATAGGCATG  
ATCTTCGAAATTTATGGATTTTTTCTCTTGTTT

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**FIGURE 92**

GGCACGAGGCTGAACCCAGCCGGCTCCATCTCAGCTTCTGGTTTCTAAGTCCATGTGCCAAA  
GGCTGCCAGGAAGGAGACGCCTTCCTGAGTCCTGGATCTTTCTTCCTTCTGGAAATCTTTGA  
CTGTGGGTAGTTATTTATTTCTGAATAAGAGCGTCCACGCATCCATGGACCTCGCGGGACTGC  
TGAAGTCTCAGTTCCTGTGCCACCTGGTCTTCTGCTACGTCTTTATTGCCTCAGGGCTAATC  
ATCAACACCATTCAGCTCTTCACTCTCCTCCTCTGGCCCATTAAACAAGCAGCTCTTCCGGAA  
GATCAACTGCAGACTGTCCTATTGCATCTCAAGCCAGCTGGTGATGCTGCTGGAGTGGTGGT  
CGGGCACGGAATGCACCATCTTCACGGACCCGCGCGCCTACCTCAAGTATGGGAAGGAAAAT  
GCCATCGTGGTTCTCAACCACAAGTTTGAAATTGACTTTCTGTGTGGCTGGAGCCTGTCCGA  
ACGCTTTGGGCTGTTAGGGGGCTCCAAGGTCCTGGCCAAGAAAGAGCTGGCCTATGTCCCAA  
TTATCGGCTGGATGTGGTACTTCACCGAGATGGTCTTCTGTTCGCGCAAGTGGGAGCAGGAT  
CGCAAGACGGTTGCCACCAGTTTGCAGCACCTCCGGGACTACCCCGAGAAGTATTTTTTTCCT  
GATTCACTGTGAGGGCACACGGTTCACGGAGAAGAAGCATGAGATCAGCATGCAGGTGGCCC  
GGGCAAGGGGCTGCCTCGCCTCAAGCATCACCTGTTGCCACGAACCAAGGGCTTCGCCATC  
ACCGTGAGGAGCTTGAGAAATGTAGTTTCAGCTGTATATGACTGTACACTCAATTTCAGAAA  
TAATGAAAATCCAACACTGCTGGGAGTCCTAAACGGAAAGAAATACCATGCAGATTTGTATG  
TTAGGAGGATCCCACCTGGAAGACATCCCTGAAGACGATGACGAGTGCTCGGCCTGGCTGCAC  
AAGCTCTACCAGGAGAAGGATGCCTTTCAGGAGGAGTACTACAGGACGGGCACCTTCCCAGA  
GACGCCCATGGTGCCCCCCCCGGCGGCCCTGGACCCTCGTGAACCTGGCTGTTTTGGGCCTCGC  
TGGTGCTCTACCCTTTCTTCCAGTTCCTGGTCAGCATGATCAGGAGCGGGTCTTCCCTGACG  
CTGGCCAGCTTCATCCTCGTCTTCTTTGTGGCCTCCGTGGGAGTTCGATGGATGATTGGTGT  
GACGGAAATTGACAAGGGCTCTGCCTACGGCAACTCTGACAGCAAGCAGAACTGAATGACT  
GACTCAGGGAGGTGTCACCATCCGAAGGGAACCTTGGGGAACCTGGTGGCCTCTGCATATCCT  
CCTTAGTGGGACACGGTGACAAAGGCTGGGTGAGCCCCTGCTGGGCACGGCGGAAGTCACGA  
CCTCTCCAGCCAGGGAGTCTGGTCTCAAGGCCGGATGGGGAGGAAGATGTTTTGTAATCTTT  
TTTTCCCCATGTGCTTTAGTGGGCTTTGGTTTTCTTTTTGTGCGAGTGTGTGTGAGAATGGC  
TGTGTGGTGAGTGTGAACTTTGTTCTGTGATCATAGAAAGGGTATTTTAGGCTGCAGGGGAG  
GGCAGGGCTGGGGACCGAAGGGGACAAGTTCCCTTTTCATCCTTTGGTGCTGAGTTTTCTGT  
AACCCTTGGTTGCCAGAGATAAAGTGAAAAGTGCTTTAGGTGAGATGACTAAATTATGCCTC  
CAAGAAAAAAAAAATTAAAGTGCTTTTCTGGGTCAAAAAAAAAAAAA

**FIGURE 93**

MDLAGLLKSQFLCHLVFCYVFIASGLIINTIQLFTLLLWPINKQLFRKINCRLSYCISSQLV  
MLLEWWSGTECTIFTDPRAYLKYGKENAIVVLNHNKFEIDFLCGWSLSERFGLLGSKVLAKK  
ELAYVPIIGWMWYFTEMVFCSRKWEQDRKTVATSLQHLRDYPEKYFFLIHCEGTRFTEKKHE  
ISMQVARAKGLPRLKHHLLPRTKGFAITVRSLRNVVSAVYDCTLNFRNNENPTLLGVNLGKK  
YHADLYVRRIPLEDIPEDDDECSAWLHKLYQEKDAFQEEYYRTGTFPETPMVPPRRPWTLVN  
WLFWASLVLYPFFQFLVSMIRSGSSLTLASFILVFFVASVGVRWMIGVTEIDKGSAYGNSDS  
KQKLND



**FIGURE 94**

CTGAGGCGGCGGTAGCATGGAGGGGGAGAGTACGTCGGCGGTGCTCTCGGGCTTTGTGCTCG  
GCGCACTCGCTTTCCAGCACCTCAACACGGACTCGGACACGGAAGGTTTTCTTCTTGGGGAA  
GTAAAAGGTGAAGCCAAGAACAGCATTACTGATTCCCAAATGGATGATGTTGAAGTTGTTTA  
TACAATTGACATTCAGAAATATATTCCATGCTATCAGCTTTTTTAGCTTTTATAATTCTTCAG  
GCGAAGTAAATGAGCAAGCACTGAAGAAAATATTATCAAATGTCAAAAAGAATGTGGTAGGT  
TGGTACAAATTCCGTCGTCATTGATCAGATCAGATCATGACGTTTAGAGAGAGGCTGCTTCACAA  
AACTTGCAGGAGCATTTTTTCAAACCAAGACCTTGTTTTTCTGCTATTAACACCAAGTATAA  
TAACAGAAAGCTGCTCTACTCATCGACTGGAACATTCTTATATAAACCTCAAAAAGGACTT  
TTTCACAGGGTACCTTTAGTGGTTGCCAATCTGGGCATGTCTGAACAACTGGGTTATAAAAC  
TGTATCAGGTTCCCTGTATGTCCACTGGTTTTAGCCGAGCAGTACAAACACACAGCTCTAAAT  
TTTTTGAAGAAGATGGATCCTTAAAGGAGGTACATAAGATAAATGAAATGTATGCTTCATTA  
CAAGAGGAATTAAAGAGTATATGCAAAAAAGTGGAAGACAGTGAACAAGCAGTAGATAAACT  
AGTAAAGGATGTAAACAGATTAAAACGAGAAATTGAGAAAAGGAGAGGAGCACAGATTCAGG  
CAGCAAGAGAGAAGAACATCCAAAAAGACCCTCAGGAGAACATTTTTCTTTGTCAGGCATTA  
CGGACCTTTTTTCCAAATTCTGAATTTCTTCATTGATGTGTTATGTCTTTAAAAAATAGACA  
TGTTTCTAAAAGTAGCTGTAACACACCACCTCTCGATGTAGTAGACAATCTGACCTTAA  
TGGTAGAACACACTGACATTCCTGAAGCTAGTCCAGCTAGTACACCACAAATCATTAGCAT  
AAAGCCTTAGACTTAGATGACAGATGGCAATTCAAGAGATCTCGGTTGTTAGATACACAAGA  
CAAACGATCTAAAGCAAATACTGGTAGTAGTAACCAAGATAAAGCATCCAAAATGAGCAGCC  
CAGAAACAGATGAAGAAATTGAAAAGATGAAGGGTTTTGGTGAATATTCACGGTCTCCTACA  
TTTTGTATCCTTTTAACTTACAAGGAGATTTTTTTTATTTGGCTGATGGGTAAAGCCAAACAT  
TTCTATTGTTTTTACTATGTTGAGCTACTTGCAGTAAGTTCATTTGTTTTTACTATGTTTAC  
CTGTTTGCAGTAATACACAGATAACTCTTAGTGCATTTACTTCACAAAGTACTTTTTCAAAC  
ATCAGATGCTTTTATTTCCAAACCTTTTTTTCACCTTTCACCTAAGTTGTTGAGGGGAAGGCT  
TACACAGACACATTCTTTAGAATTGGAAAAGTGAGACCAGGCACAGTGGCTCACACCTGTAA  
TCCCAGCACTTAGGGAAGACAAGTCAGGAGGATTGATTGAAGCTAGGAGTTAGAGACCAGCC  
TGGGCAACGTATTGAGACCATGTCTATTAAAAAATAAAATGGAAAAGCAAGAATAGCCTTAT  
TTTCAAAATATGGAAAGAAATTTATATGAAAATTTATCTGAGTCATTAAAATTCTCCTTAAG  
TGATACTTTTTTAGAAGTACATTATGGCTAGAGTTGCCAGATAAAATGCTGGATATCATGCA  
ATAAATTTGCAAAACATCATCTAAAATTTAAAAAATAAAAAAAAAAAAAAAAAAAAAA

**FIGURE 95**

MEGESTSAVLSGFVLGALAFQHLNTDSDTEGFLLGGEVKGEAKNSITDSQMDDVEVVYTIDIQ  
KYIPCYQLFSFYNSSGEVNEQALKKILSNVKKNVVGWYKFRRHSDQIMTFRERLLHKNLQEH  
FSNQDLVFLLLTPSIITESCSTHRLEHSLYKPQKGLFHRVPLVVANLGMSEQLGKYKTVSGSC  
MSTGFSRAVQTHSSKFFEEEDGSLKEVHKINEMYASLQEELKSICKKVEDSEQAVDKLVKDVN  
RLKREIEKRRGAQIQAAAREKNIQKDPQENIFLCQALRTFFPNSEFLHSCVMSLKNRHVSKSS  
CNYNHHLDVVDNLTLMVEHTDIPEASPASTPQIIKHKALDLDLDRWQFKRSRLDQDKRSKA  
NTGSSNQDKASKMSSPETDEEIEKMKGFGEYSRSPTF

**FIGURE 96**

GGCACAGCCGCGCGGCGGAGGGCAGAGTCAGCCGAGCCGAGTCCAGCCGGACGAGCGGACCA  
GCGCAGGGCAGCCCAAGCAGCGCGCAGCGAACGCCCCGCGCCGCCACACCCTCTGCGGTCC  
CCGCGGCGCCTGCCACCCTTCCCTCCTTCCCCGCGTCCCCGCTCGCCGGCCAGTCAGCTTG  
CCGGGTTGCTGCCCCGCGAAACCCCGAGGTCACCAGCCCGCGCCTCTGCTTCCCTGGGCCC  
CGCGCCGCTCCACGCCCTCCTTCTCCCCTGGCCCCGGCGCCTGGCACCGGGGACCGTTGCCT  
GACGCGAGGCCCAGCTCTACTTTTCGCCCCGCGTCTCCTCCGCCTGCTCGCCTCTTCCACCA  
ACTCCAACCTCCTTCTCCCTCCAGCTCCACTCGCTAGTCCCCGACTCCGCCAGCCCTCGGCCC  
GCTGCCGTAGCGCCGCTTCCCGTCCGGTCCCAAAGGTGGGAACGCGTCCGCCCCGGCCCCGCA  
CCATGGCACGGTTCGGCTTGCCCCGCGCTTCTCTGCACCCTGGCAGTGCTCAGCGCCGCGCTG  
CTGGCTGCCGAGCTCAAGTCGAAAAGTTGCTCGGAAGTGCGACGTCTTTACGTGTCAAAGG  
CTTCAACAAGAACGATGCCCCCTCCACGAGATCAACGGTGATCATTTGAAGATCTGTCCCC  
AGGGTTCTACCTGCTGCTCTCAAGAGATGGAGGAGAAGTACAGCCTGCAAAGTAAAGATGAT  
TTCAAAAGTGTGGTCAGCGAACAGTGCAATCATTTGCAAGCTGTCTTTGCTTCACGTTACAA  
GAAGTTTGATGAATTCTTCAAAGAACTACTTGAAAATGCAGAGAAATCCCTGAATGATATGT  
TTGTGAAGACATATGGCCATTTATACATGCAAAATTCTGAGCTATTTAAAGATCTCTTCGTA  
GAGTTGAAACGTTACTACGTGGTGGGAAATGTGAACCTGGAAGAAATGCTAAATGACTTCTG  
GGCTCGCCTCCTGGAGCGGATGTTCCGCCTGGTGAACCTCCAGTACCACTTTACAGATGAGT  
ATCTGGAATGTGTGAGCAAGTATACGGAGCAGCTGAAGCCCTTCGGAGATGTCCCTCGCAA  
TTGAAGCTCCAGGTTACTCGTGCTTTTGTTAGCAGCCCGTACTTTCGCTCAAGGCTTAGCGGT  
TGCGGGAGATGTCGTGAGCAAGGTCTCCGTGGTAAACCCACAGCCAGTGTAACCATGCCC  
TGTTGAAGATGATCTACTGCTCCCACTGCCGGGGTCTCGTGACTGTGAAGCCATGTTACAAC  
TACTGCTCAAACATCATGAGAGGCTGTTTGGCCAACCAAGGGGATCTCGATTTTGAATGGAA  
CAATTTCATAGATGCTATGCTGATGGTGGCAGAGAGGCTAGAGGGTCCTTTCAACATTGAAT  
CGGTCATGGATCCCATCGATGTGAAGATTTCTGATGCTATTATGAACATGCAGGATAATAGT  
GTTCAAGTGTCTCAGAAGGTTTTCCAGGGATGTGGACCCCCCAAGCCCTCCAGCTGGACG  
AATTTCTCGTTCCATCTCTGAAAGTGCCTTCAGTGCTCGCTTCAGACCACATCACCCCGAGG  
AACGCCCAACCACAGCAGCTGGCACTAGTTTGGACCGACTGGTTACTGATGTCAAGGAGAAA  
CTGAAACAGGCCAAGAAATTCTGGTCCTCCCTTCCGAGCAACGTTTGCAACGATGAGAGGAT  
GGCTGCAGGAAACGGCAATGAGGATGACTGTTGGAATGGGAAAGGCAAAAGCAGGTACCTGT  
TTGCAGTGACAGGAAATGGATTAGCCAACCAGGGCAACAACCCAGAGGTCCAGGTTGACACC  
AGCAAACCAGACATACTGATCCTTCGTCAAATCATGGCTCTTCGAGTGATGACCAGCAAGAT  
GAAGAATGCATACAATGGGAACGACGTGGACTTCTTTGATATCAGTGATGAAAGTAGTGGAG  
AAGGAAGTGGAAGTGGCTGTGAGTATCAGCAGTGCCCTTCAGAGTTTGACTACAATGCCACT  
GACCATGCTGGGAAGAGTGCCAATGAGAAAGCCGACAGTGCTGGTGTCCGTCCTGGGGCACA  
GGCCTACCTCCTCACTGTCTTCTGCATCTTGTTCTTGGTTATGCAGAGAGAGTGAGATAAT  
TCTCAAACCTCTGAGAAAAAGTGTTTCATCAAAAAGTTAAAAGGCACCAGTTATCACTTTTCTA  
CCATCCTAGTGACTTTGCTTTTTTAAATGAATGGACAACAATGTACAGTTTTTACTATGTGGC  
CACTGGTTTAAGAAGTGCTGACTTTGTTTTCTCATTTCAGTTTTGGGAGGAAAAGGGACTGTG  
CATTGAGTTGGTTCCTGCTCCCCCAAACCATGTAAACGTGGCTAACAGTGTAAGGTACAGAA  
CTATAGTTAGTTGTGCATTTGTGATTTTATCACTCTATTATTGTTTGTATGTTTTTTCTC  
ATTTTCGTTTGTGGGTTTTTTTTTCCAACGTGATCTCGCCTTGTTTCTTACAAGCAAACAG  
GGTCCCTTCTTGGCACGTAAACATGTACGTATTTCTGAAATATTAAATAGCTGTACAGAAGCA  
GGTTTTATTTATCATGTTATCTTATTAAAGAAAAAGCCCCAAAAAGC

**FIGURE 97**

MARFGLPALLCTLAVLSAALLAELKSKSCSEVRRLYVSKGFNKNDAPLHEINGDHLKICPQ  
GSTCCSQEMEKEYSLQSKDDFKSVVSEQCNHLQAVFASRYKKFDEFFKELLENAEKSLNDMF  
VKTYGHLYMQNSELFKDLFVELKRYVVGNNLEEMLNDFWARLLERMFRLVNSQYHFTDEY  
LECVSKYTEQLKPFQDVPRKLKLQVTRAFVAARTFAQGLAVAGDVVSKVSVVNPTAQCTHAL  
LKMIYCSHCRGLVTVKPCYNYCSNIMRGCLANQGDLDFFWNNFIDAMLMVAERLEGPFNIES  
VMDPIDVKISDAIMNMQDNSVQVSQKVFQCGPPKPLPAGRISRSISESAFSARFRPHHPEE  
RPTTAAGTSLDRLVTDVKEKLKQAKKFWSSLPSNVCNDERMAAGNGNEDDCWNGKGKSRYL  
AVTGNGLANQGNNPEVQVDTSKPDILILRQIMALRVMTSKMKNAYNNGNDVDFFDISDESSGE  
GSGSGCEYQQCPSEFDYNATDHAGKSANEKADSAGVRPGAQAYLLTVFCILFLVMQREWR



**FIGURE 98**

CTCGCCCTCAAATGGGAACGCTGGCCTGGGACTAAAGCATAGACCACCAGGCTGAGTATCCT  
GACCTGAGTCATCCCCAGGGATCAGGAGCCTCCAGCAGGGAACCTTCCATTATATTCTTCAA  
GCAACTTACAGCTGCACCGACAGTTGCGATGAAAGTTCTAATCTCTTCCCTCCTCCTGTTGC  
TGCCACTAATGCTGATGTCCATGGTCTCTAGCAGCCTGAATCCAGGGGTGCGCCAGAGGCCAC  
AGGGACCGAGGCCAGGCTTCTAGGAGATGGCTCCAGGAAGGCGGCCAAGAATGTGAGTGCAA  
AGATTGGTTCCTGAGAGCCCCGAGAAGAAAATTCATGACAGTGTCTGGGCTGCCAAAGAAGC  
AGTGCCCCTGTGATCATTTCAAGGGCAATGTGAAGAAAACAAGACACCAAAGGCACCACAGA  
AAGCCAAACAAGCATTCCAGAGCCTGCCAGCAATTTCTCAAACAATGTCAGCTAAGAAGCTT  
TGCTCTGCCTTTGTAGGAGCTCTGAGCGCCCACTCTTCCAATTAAACATTCTCAGCCAAGAA  
GACAGTGAGCACACCTACCAGACACTCTTCTTCTCCACCTCACTCTCCCACTGTACCCACC  
CCTAAATCATTTCCAGTGCTCTCAAAAAGCATGTTTTTCAAGATCATTTTGTTTGTTGCTCTC  
TCTAGTGTCTTCTTCTCTCGTCAGTCTTAGCCTGTGCCCTCCCCTTACCCAGGCTTAGGCTT  
AATTACCTGAAAGATTCCAGGAAACTGTAGCTTCCTAGCTAGTGTCATTTAACCTTAAATGC  
AATCAGGAAAGTAGCAAACAGAAGTCAATAAATATTTTTTAAATGTCAAAAAAAAAAAAAAAAAA

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**FIGURE 99**

MKVLISLLLLLPLMLMSMVSSSLNPGVARGHRDRGQASRRWLQEGGQECECKDWFLRAPRR  
KFMTVSGLPKKQCPCDHFKGNVKKTRHQRRHRKPNKHSRACQQFLKQCQLRSFALPL

**FIGURE 100**

AATGGCTGTCTTAGTACTTCGCCTGACAGTTGTCCTGGGACTGCTTGTCTTATTCTTGACCT  
GCTATGCAGACGACAAACCAGACAAGCCAGACGACAAGCCAGACGACTCGGGCAAAGACCCA  
AAGCCAGACTTCCCCAAATTCCTAAGCCTCCTGGGCACAGAGATCATTGAGAATGCAGTCGA  
GTTTCATCCTCCGCTCCATGTCCAGGAGCACAGGATTTATGGAATTTGATGATAATGAAGGAA  
AACATTTCATCAAAGTGACATCCTCAGGACACACCCATGTGGCTCCTGGACAATCCAAGAGCA  
GCCAAATCCTGCTTTTCCAGTTTGGCTCCACAAGTCCTCCAGGACAGAGCCCTCAAAGCAAC  
TCCCAACGAGTTCTCAGGATTCAGGCTCTGGCTTCAACCAAACAGAACTCATTTTGAACACC  
CTGACTGCATTTTTTGCTTTTAGAAAGTTAGAATAAATATGGCGCTTTGGGATCACATAGTTG  
ATGGAGAGGAAA

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**FIGURE 101**

MAVLVLRLTVVLGLLVLFLTCTYADDKPKDPDDSGKDPKPDFPKFLSLLGTEIIENAVE  
FILRSMSRSTGFMEFDDNEGKHSSK



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**FIGURE 102**

GGACGCCAGCGCCTGCAGAGGCTGAGCAGGGAAAAAGCCAGTGCCCCAGCGGAAGCACAGCT  
CAGAGCTGGTCTGCCATGGACATCCTGGTCCCACCTCCTGCAGCTGCTGGTGCTGCTTCTTAC  
CCTGCCCCCTGCACCTCATGGCTCTGCTGGGCTGCTGGCAGCCCCCTGTGCAAAAGCTACTTCC  
CCTACCTGATGGCCGTGCTGACTCCCAAGAGCAACCGCAAGATGGAGAGCAAGAAACGGGAG  
CTCTTCAGCCAGATAAAGGGGCTTACAGGAGCCTCCGGGAAAGTGGCCCTACTGGAGCTGGG  
CTGCGGAACCGGAGCCAACTTTCAGTTCTACCCACCGGGCTGCAGGGTCACCTGCCTAGACC  
CAAATCCCCACTTTGAGAAGTTCCTGACAAAGAGCATGGCTGAGAACAGGCACCTCCAATAT  
GAGCGGTTTGTGGTGGCTCCTGGAGAGGACATGAGACAGCTGGCTGATGGCTCCATGGATGT  
GGTGGTCTGCACTCTGGTGCTGTGCTCTGTGCAGAGCCCAAGGAAGGTCCTGCAGGAGGTCC  
GGAGAGTACTGAGACCGGGAGGTGTGCTCTTTTTCTGGGAGCATGTGGCAGAACCATATGGA  
AGCTGGGCCTTCATGTGGCAGCAAGTTTTCGAGCCCACCTGGAAACACATTGGGGATGGCTG  
CTGCCTCACCAGAGAGACCTGGAAGGATCTTGAGAACGCCCAGTTCTCCGAAATCCAAATGG  
AACGACAGCCCCCTCCCTTGAAGTGGCTACCTGTTGGGCCCCACATCATGGGAAAGGCTGTC  
AAACAATCTTTCCCAAGCTCCAAGGCACTCATTTGCTCCTTCCCCAGCCTCCAATTAGAACA  
AGCCACCCACCAGCCTATCTATCTTCCACTGAGAGGGACCTTAGCAGAATGAGAGAAGACATT  
CATGTACCACCTACTAGTCCCTCTCTCCCCAACCTCTGCCAGGGCAATCTCTAACTTCAATC  
CCGCCTTCGACAGTGAAAAAGCTCTACTTCTACGCTGACCCAGGGAGGAAACACTAGGACCC  
TGTTGTATCCTCAACTGCAAGTTTCTGGACTAGTCTCCCAACGTTTGCCTCCCAATGTTGTC  
CCTTTCCTTCGTTCCCATGGTAAAGCTCCTCTCGCTTTCCTCCTGAGGCTACACCCATGCGT  
CTCTAGGAACCTGGTCACAAAAGTCATGGTGCCTGCATCCCTGCCAAGCCCCCTGACCCTCT  
CTCCCCACTACCACCTTCTTCCTGAGCTGGGGGCACCAGGGAGAATCAGAGATGCTGGGGAT  
GCCAGAGCAAGACTCAAAGAGGCAGAGGTTTTGTTCTCAAATATTTTTTAATAAATAGACGA  
AACCACG

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**FIGURE 103**

MDILVPLLQLLVLLLTLPPLHLMALLGCWQPLCKSYFPYLMAVLTPKSNRKMESKKRELFSQL  
KGLTGASGKVALLELGCGTGANFQFYPPGCRVTCLDPNPHFEKFLTKSMAENRHLQYERFVV  
APGEDMRQLADGSMDVVVCTLVLCVQSPRKVLQEVRRVLRPGGVLFWEHVAEPYGSWAFM  
WQQVFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKWLPVGPHIMGKAVKQSFP  
SSKALICSFPSLQLEQATHQPIYLPLRGT

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**FIGURE 104**

GTGGGATTTATTTGAGTGCAAGATCGTTTTCTCAGTGGTGGTGGGAAGTTGCCTCATCGCAGG  
CAGATGTTGGGGCTTTGTCCGAACAGCTCCCCTCTGCCAGCTTCTGTAGATAAGGGTTAAAA  
ACTAATATTTATATGACAGAAGAAAAAGATGTCATTCCGTAAAGTAAACATCATCATCTTGG  
TCCTGGCTGTTGCTCTCTTCTTACTGGTTTTGCACCATAACTTCCTCAGCTTGAGCAGTTTG  
TTAAGGAATGAGGTTACAGATTCAGGAATTGTAGGGCCTCAACCTATAGACTTTGTCCCAA  
TGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCTGTGGTCATCGCTGCATCTG  
AAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTTCAGCACAACACTCGCTCCAAT  
GTGATTTTCTACATTGTTACTCTCAACAATACAGCAGACCATCTCCGGTCCTGGCTCAACAG  
TGATTCCCTGAAAAGCATCAGATACAAAATTGTCAATTTTGACCCTAAACTTTTGGAAGGAA  
AAGTAAAGGAGGATCCTGACCAGGGGGAATCCATGAAACCTTTAACCTTTGCAAGGTTCTAC  
TTGCCAATTCTGGTTCCCAGCGCAAAGAAGGCCATATACATGGATGATGATGTAATTGTGCA  
AGGTGATATTCTTGCCCTTTACAATACAGCACTGAAGCCAGGACATGCAGCTGCATTTTCAG  
AAGATTGTGATTCAGCCTCTACTAAAGTTGTCATCCGTGGAGCAGGAAACCAGTACAATTAC  
ATTGGCTATCTTGACTATAAAAAGGAAAGAATTCGTAAGCTTTCCATGAAAGCCAGCACTTG  
CTCATTTAATCCTGGAGTTTTTTGTTGCAAACCTGACGGAATGGAAACGACAGAATATAACTA  
ACCAACTGGAAAAATGGATGAAACTCAATGTAGAAGAGGGACTGTATAGCAGAACCCTGGCT  
GGTAGCATCACAACACCTCCTCTGCTTATCGTATTTTATCAACAGCACTCTACCATCGATCC  
TATGTGGAATGTCCGCCACCTTGGTTCCAGTGCTGGAAAACGATATTCACCTCAGTTTGTA  
AGGCTGCCAAGTTACTCCATTGGAATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATAT  
ACTGATGTTTGGGAAAAATGGTATATTCCAGACCCAACAGGCAAATTCAACCTAATCCGAAG  
ATATACCGAGATCTCAAACATAAAGTGAACAGAAATTTGAACTGTAAGCAAGCATTCTCAG  
GAAGTCCTGGAAGATAGCATGCATGGGAAGTAACAGTTGCTAGGCTTCAATGCCTATCGGTA  
GCAAGCCATGGAAAAAGATGTGTCAGCTAGGTAAAGATGACAAACTGCCCTGTCTGGCAGTC  
AGCTTCCCAGACAGACTATAGACTATAAATATGTCTCCATCTGCCTTACCAAGTGTTTTCTT  
ACTACAATGCTGAATGACTGGAAAGAAGAACTGATATGGCTAGTTCAGCTAGCTGGTACAGA  
TAATTCAAACTGCTGTTGGTTTTAATTTTGTAACCTGTGGCCTGATCTGTAAATAAACTT  
ACATTTTTC

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**FIGURE 105**

MSFRKVNIIILVLAVALFLLVLHHNFLSLSSLLRNEVTDSGIVGPQPIDFVPNALRHAVDGR  
QEEIPVVIAASEDRLGGAIAAINSIOHNTRSNVIFYIVTLNNTADHLRSWLNSDSLKSIRYK  
IVNFDPKLLEGKVKEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIQGDILALYNT  
ALKPGHAAAFSEDCDSASTKV VIRGAGNQYNYIGYLDYKKERIRKLSMKASTCSFNPGVFVA  
NLTEWKRQNI TNQLEKWMKLNVEEGLYSRTLGSITTPLLIVFYQQHSTIDPMWNVRHLGS  
SAGKRYSPQFVKA AKLLHWNGHLKPWGRTASYTDVWEKWI PDPTGKFNLIRRYTEISNIK



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**FIGURE 106**

TGGTTTTTGCCCCATAAATTCCCTCAGCTTGAGCAGTTTGTTAAGGAATGAGGTTACAGATT  
CAGGAATTNTAGGNCCTCAACCTNTAGANTTTGTCCCAAATGTTCTCCGACATGCAGTAGAT  
GGGAGACAAGAGGAGATTCTGTGGTCATCGCTGCATNTGAAGACAGGCTTGGGGGGGCCAT  
TGCAGCTATAAACAGCATTTCAGCACAACACTCGNTCCAATGTGATTTTCTACATTGTTACTC  
TCAACAATACAGCAGACCATNTCCGGTCCTGGNTCAACAGTGATTCCCTGAAAAGCATCAGA  
TACAAAATTGTCAATTTTGACCCTAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCA  
GGGGGAATCCATGAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCG  
CAAAGAAGGCCATATACATGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTAC  
AATACAGCACTGAAGCCAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTCAGCCTCTAC  
TAAAGTTGTCATCCGTGGAGCAGGAAA

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**FIGURE 107**

CGACGCTCTAGCGGTACCGCTGCGGGCTGGCTGGGCGTAGTGGGGCTGCGCGGCTGCCACG  
GAGCTAGAGGGCAAGTGTGCTCGGCCCAGCGTGCAGGGAACGCGGGCGGCCAGACAACGGGC  
TGGGCTCCGGGGCCTGCGGCGCGGGCGCTGAGCTGGCAGGGCGGGTCTGGGGCGCGGGCTGCA  
TCCGCATCTCCTCCATCGCCTGCAGTAAGGGCGGCCGCGGCGAGCCTTTGAGGGGAACGACT  
TGTCTGGAGCCCTAACCAGGGGTGTCTCTGAGCCTGGTGGGATCCCCGGAGCGTCACATCACT  
TTCCGATCACTTCAAAGTGGTTAAAACTAATATTTATATGACAGAAGAAAAAGATGTCATT  
CCGTAAAGTAAACATCATCATCTTGGTCCTGGGCTGTTGCTCTCTTCTTACTGGTTTTGCAC  
CATAACTTCCTCAGCTTGAGGCAGTTTGTTAAGGAATGAGGTTACAGATTCAGGAATTGTAG  
GGCCTCAACCTATAGGACTTTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGA  
GGAGATTCCTGTGGTCATCGCTGCATCTGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAA  
ACAGCATTTCAGCACAACACTCGCTCCAATGTGATTTTCTACATTGTTACTCTCAACAATACA  
GCAGACCATCTCCGGTCCTGGGCTCAACAGTGATTCCTGAAAAGCATCAGATACAAAATTG  
TCAATTTTGACCCTAAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCAGGGGGAATCC  
ATGAAACCTTTAACCTTTGCAAGGTTCTACTTGCCAATTCTGGGTTCACAGCGCAAAGAAGG  
CCATATACATGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGCA  
CTGAAGCCAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTCAGCCTCTACTAAAGTTGT  
CATCCGTGGAGCAGGAAACCAGTACAATTACATTGGCTATCTTGACTATAAAAAGGAAAGAA  
TTCGTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTTTTGTGTTGCAAAC  
CTGACGGAATGGAAACGACAGAATATACTAACCAACTGGAAAAATGGATGAAACTCAATGT  
AGAAGAGGGACTGTATAGCAGAACCCTGGCTGGTAGCATCACACACCTCCTCTGCTTATCG  
TATTTTATCAACAGCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGGTTCCAGT  
GCTGGAAAACGATATTCACCTCAGTTTGTAAGGCTGCCAAGTTACTCCATTGGAATGGACA  
TTTGAAGCCATGGGGAAGGACTGCTTCATATACTGATGTTTGGGGAAAAATGGTATATTCCA  
GACCCAACAGGCAAATTCAACCTAATCCGAAGATATACCGAGATCTCAAACATAAAGTGAAA  
CAGAATTTGAACTGTAAGCAAGCATTTCTCAGGAAGTCCTGGAAGATAGCATGCGTGGGAAG  
TAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAAGATGTGTCAGCTAG  
GTAAAGATGACAACTGCCCTGTCTGGCAGTCAGCTTCCCAGACAGACTATAGACTATAAAT  
ATGTCTCCATCTGCCTTACCAAGTGTTTTCTTACTACAATGCTGAATGACTGGAAAGAAGAA  
CTGATATGGCTAGTTCAGCTAGCTGGTACAGATAATTCAAACTGCTGTTGGTTTTAATTTT  
GTAACCTGTGGCCTGATCTGTAAATAAACTTACATTTTTTCAATAGGTAAAAA

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**FIGURE 108**

CTGCAGGTAGACATCTCCACTGCCCAGGAATCACTGAGCGTGCAGACAGCACAGCCTCCTCT  
GAAGGCCGGCCATACCAGAGTCCTGCCTCGGCATGGGCCTCACCATTGAGGCAGCTCCACTG  
TCTGTGCTGGTCTGAGGGTGCTGCCTGTCATGGGGGCAGCCATCTCCCAGGGGGCCCTCATC  
GCCATCGTCTGCAACGGTCTCGTGGGCTTCTTGCTGCTGCTGCTCTGGGTCATCCTCTGCTG  
GGCCTGCCATTCTCGTCTGCCGACGTTGACTCTCTCTCTGAATCCAGTCCCAACTCCAGCCC  
TGGCCCCTGTCCTGAGAAGGCCCCACCACCCCAGAAGCCCAGCCATGAAGGCAGCTACCTGC  
TGCAGCCCTGAAGGCCCCTGGCCTAGCCTGGAGCCCAGGACCTTAGTCCACCTCACCTAGAG  
CCTGGAATTAGGATCCCAGAGTTCAGCCAGCCTGGGGTCCAGAACTCAAGAGTCCGCCTGCT  
TGGAGCTGGACCCAGCGGCCCAGAGTCTAGCCAGCTTGGCTCCAATAGGAGCTCAGTGGCCC  
TAAGGAGATGGGCCTGGGGTGGGGGCTTATGAGTTGGTGCTAGAGCCAGGGCCATCTGGACT  
ATGCTCCATCCCAAGGGCCAAGGGTCAGGGGCCGGGTCCACTCTTTCCCTAGGCTGAGCACC  
TCTAGGCCCTCTAGGTTGGGGAAGCAAACCTGGAACCCATGGCAATAATAGGAGGGTGTCCAG  
GCTGGGCCCCTCCCCTGGTCCTCCCAGTGTTTGCTGGATAATAAATGGAACCTATGGCTCTAA  
AAAAAAAAAAAAAAAAAAAA

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**FIGURE 109**

MGA AISQ GALIA IVCNGLVGFL LLLWVILCWACHSRLPTLTLSLNPVPTPALAPVLRPHH  
PRSPAMKAATCCSPEGPWPSLEPRT



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**FIGURE 110**

GTTTGAATTCCTTCAACTATACCCACAGTCCAAAAGCAGACTCACTGTGTCCCAGGCTACCA  
GTTCCCTCCAAGCAAGTCATTTCCCTTATTTAACCGATGTGTCCCTCAAACACCTGAGTGCTA  
CTCCCTATTTGCATCTGTTTTGATAAATGATGTTGACACCCTCCACCGAATTCTAAGTGGAA  
TCATGTCGGGAAGAGATACAATCCTTGGCCTGTGTATCCTCGCATTAGCCTTGTCTTTGGCC  
ATGATGTTTACCTTCAGATTCATCACCACCCTTCTGGTTCACATTTTCATTTCAATTGGTTAT  
TTTGGGATTGTTGTTTGTCTGCGGTGTTTTATGGTGGCTGTATTATGACTATACCAACGACC  
TCAGCATAGAATTGGACACAGAAAGGGAAAATATGAAGTGCGTGCTGGGGTTTGCTATCGTA  
TCCACAGGCATCACGGCAGTGCTGCTCGTCTTGATTTTTTGTCTCAGAAAGAGAATAAAATT  
GACAGTTGAGCTTTTCCAAATCACAAATAAAGCCATCAGCAGTGCTCCCTTCCTGCTGTTCC  
AGCCACTGTGGACATTTGCCATCCTCATTTTTCTTCTGGGTCTCTGGGTGGCTGTGCTGCTG  
AGCCTGGGAACTGCAGGAGCTGCCCAGGTTATGGAAGGCGGCCAAGTGGAATATAAGCCCCT  
TTCGGGCATTTCGGTACATGTGGTCGTACCATTTAATTGGCCTCATCTGGACTAGTGAATTCA  
TCCTTGCGTGCCAGCAAATGACTATAGCTGGGGCAGTGGTTACTTGTTATTTCAACAGAAGT  
AAAAATGATCCTCCTGATCATCCCATCCTTTCGTCTCTCTCCATTCTCTTCTTCTACCATCA  
AGGAACCGTTGTGAAAGGGTCATTTTTTAATCTCTGTGGTGAGGATTCCGAGAATCATTGTCA  
TGTACATGCAAAACGCACTGAAAGAACAGCAGCATGGTGCATTGTCCAGGTACCTGTTCCGA  
TGCTGCTACTGCTGTTTCTGGTGTCTTGACAAATACCTGCTCCATCTCAACCAGAATGCATA  
TACTACAACCTGCTATTAATGGGACAGATTTCTGTACATCAGCAAAAGATGCATTCAAAATCT  
TGTCCAAGAACTCAAGTCACTTTACATCTATTAAGTCTTTGGAGACTTCATAATTTTTCTA  
GGAAAGGTGTTAGTGGTGTGTTTCACTGTTTTTGGAGGACTCATGGCTTTTAACTACAATCG  
GGCATTCCAGGTGTGGGCAGTCCCTCTGTTATTGGTAGCTTTTTTTGCCTACTTAGTAGCCC  
ATAGTTTTTTTATCTGTGTTTGAAACTGTGCTGGATGCACTTTTCCTGTGTTTTGCTGTTGAT  
CTGGAAACAAATGATGGATCGTCAGAAAAGCCCTACTTTATGGATCAAGAATTTCTGAGTTT  
CGTAAAAAGGAGCAACAAATTAAACAATGCAAGGGCACAGCAGGACAAGCACTCATTAAGGA  
ATGAGGAGGGAAACAGAACTCCAGGCCATTGTGAGATAGATAACCCATTTAGGTATCTGTACCT  
GGAAACATTTCTTCTAAGAGCCATTTACAGAATAGAAGATGAGACCACTAGAGAAAAGTT  
AGTGAATTTTTTTTTTAAAGACCTAATAAACCTATTCTTCCTCAAAA

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**FIGURE 111**

MSGRDTILGLCILALALSLAMMFTFRFITTLVHIFISLVILGLLFVCGVLWWLYDYDTNDL  
SIELDTERENMKCVLGFAIVSTGITAVLLVLIFVLRKRIKLTVELFQITNKAISSAPFLLFQ  
PLWTFAILIFFWVLWVAVLLSLGTAGAAQVMEGGQVEYKPLSGIRYMWSYHLIGLIWTSEFI  
LACQQMTIAGAVVTCYFNRSKNDPPDHPILSSLSILFFYHQGTVVKGSFLISVVRIPRIIVM  
YMQNALKEQQHGALSRYLFRCCYCCFWCLDKYLLHLNQNAYTTTAINGTDFCTSAKDAFKIL  
SKNSSHFTSINCFGDFIIFLGKVLVVCFTVFGGLMAFNYNRAFQVWAVPLLVAFFAYLVAH  
SFLSVFETVLDALFLCFAVDLETNDGSSEKPYFMDQEFLSFVKRSNKLNNARAQQDKHSLRN  
EEGTELQAIVR

## FIGURE 112

[illegible]

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**FIGURE 113**

MRTVVLTMKASVIEMFLVLLVTGVHSNKETAKKIKRPKFTVPQINCDVKAGKIIDPEFIVKC  
PAGCQDPKYHVYGTDVYASYSSVCGAAVHSGVLDNSGGKILVRKVAGQSGYKGSYSNGVQSL  
SLPRWRESFIVLESKPKKGVTPSALTYSSSKSPAAQAGETTKAYQRPPIPGTTAQPVTLMQ  
LLAVTVAVATPTTLPRPSPSAASTTSIPRPQSVGHRSEQEMDLWSTATYTSSQNRPRADPGIQ  
RQDPGGAFFQKPVGADVSLGLVPKEELSTQSLEPVSLGDPNCKIDLSFLIDGSTSIGKRRFR  
IQKQLLADVAQALDIGPAGPLMGVVQYGDNPATHFNLKTHNTSRDLKTAIEKITQRGGLSNV  
GRAISFVTKNFFSKANGNRSGAPNVVVVMVDGWPTDKVEEASRLARESGINIFFITIEGAAE  
NEKQYVVEPNFANKAVCRTNGFYSLHVQSWFGLHKTLOPLVKRVCDTDRLACSKTCLNSADI  
GFVIDGSSSVGTGNFRTVLQFVTNLTKEFEISDTDRIGAVQYTYEQRLFGFDKYSSKPD  
LNAIKRVGYWSGGTSTGAAINFALEQLFKKSKPNKRKLMILITDGRSYDDVRIPAMAAHLKG  
VITYAIGVAWAAQEELEVIATHPARDHSFFVDEFDNLHQYVPRIIQNICTEFNSQPRN



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**FIGURE 114**

CAGGATGAACTGGTTGCAGTGGCTGCTGCTGCTGCGGGGGCGCTGAGAGGACACGAGCTCTA  
TGCCTTTCCGGCTGCTCATCCCGCTCGGCCTCCTGTGCGCGCTGCTGCCTCAGCACCATGGT  
GCGCCAGGTCCCGACGGCTCCGCGCCAGATCCCGCCCACTACAGTTTTTCTCTGACTCTAAT  
TGATGCACTGGACACCTTGCTGATTTTGGGGAATGTCTCAGAATTCCAAAGAGTGGTTGAAG  
TGCTCCAGGACAGCGTGGACTTTGATATTGATGTGAACGCCTCTGTGTTTGAAACAAACATT  
CGAGTGGTAGGAGGACTCCTGTCTGCTCATCTGCTCTCCAAGAAGGCTGGGGTGGAAGTAGA  
GGCTGGATGGCCCTGTTCCGGGCCTCTCCTGAGAATGGCTGAGGAGGCGGCCCCGAAAACCTCC  
TCCCAGCCTTTCAGACCCCCACTGGCATGCCATATGGAACAGTGAACCTTACTTCATGGCGTG  
AACCCAGGAGAGACCCCTGTCACCTGTACGGCAGGGATTGGGACCTTCATTGTTGAATTTGC  
CACCTTGAGCAGCCTCACTGGTGACCCGGTGTTCTGAAGATGTGGCCAGAGTGGCTTTGATGC  
GCCTCTGGGAGAGCCGGTCAGATATCGGGCTGGTCGGCAACCACATTGATGTGCTCACTGGC  
AAGTGGGTGGCCAGGACGCAGGCATCGGGGCTGGCGTGGACTCCTACTTTGAGTACTTGGT  
GAAAGGAGCCATCCTGCTTCAGGATAAGAAGCTCATGGCCATGTTCTAGAGTATAACAAAG  
CCATCCGGAACCTACACCCGCTTCGATGACTGGTACCTGTGGGTTCAGATGTACAAGGGGACT  
GTGTCCATGCCAGTCTTCCAGTCCTTGGAGGCCTACTGGCCTGGTCTTCAGAGCCTCATTGG  
AGACATTGACAATGCCATGAGGACCTTCCTCAACTACTACACTGTATGGAAGCAGTTTGGGG  
GGCTCCCGGAATTCTACAACATTCCTCAGGGATACACAGTGGAGAAGCGAGAGGGGCTACCCA  
CTTCGGCCAGAACTTATTGAAAGCGCAATGTACCTCTACCGTGCCACGGGGGATCCCACCCT  
CCTAGAACTCGGAAGAGATGCTGTGGAATCCATTGAAAAAATCAGCAAGGTGGAGTGCGGAT  
TTGCAACAATCAAAGATCTGCGAGACCACAAGCTGGACAACCGCATGGAGTCGTTCTTCCTG  
GCCGAGACTGTGAAATACCTCTACCTCCTGTTTGACCCAACCAACTTCATCCACAACAATGG  
GTCCACCTTCGACGCGGTGATCACCCCTATGGGGAGTGCATCCTGGGGGCTGGGGGGGTACA  
TCTTCAACACAGAAGCTCACCCCATCGACCTTGCCGCCCTGCACTGCTGCCAGAGGCTGAAG  
GAAGAGCAGTGGGAGGTGGAGGACTTGATGAGGGAATTCTACTCTCTCAAACGGAGCAGGTC  
GAAATTTAGAAAAACACTGTTAGTTCGGGGCCATGGGAACCTCCAGCAAGGCCAGGAACAC  
TCTTCTCACCAGAAAACCATGACCAGGCAAGGGAGAGGAAGCCTGCCAAACAGAAGGTCCCA  
CTTCTCAGCTGCCCCAGTCAGCCCTTCACCTCCAAGTTGGCATTACTGGGACAGGTTTTCT  
AGACTCCTCATATACCACTGGATAATTTTTTTATTTTTTATTTTTTTTGAGGCTAAACTATAATA  
AATTGCTTTTGGCTATCATAAAA

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**FIGURE 115**

MPFRLLIPLGLLCALLPQHHGAPGPDGSAPDPAHYSFSLTLIDALDTLLILGNVSEFORVVE  
VLQDSVDFDIDVNASVFETNIRVVGGLLSAHL LSKKAGVEVEAGWPCSGPLL RMAEEAARKL  
LPAFQTPTGMPYGTVNLLHGVNPGETPVTCTAGIGTFIVEFATLSSLTGDPVFEDVARVALM  
RLWESRSDIGLVGNHIDVLTGKWVAQDAGIGAGVDSYFEYLVKGAILLQDKKLMAMFLEYNK  
AIRNYTRFDDWYLVWQMYKGTVSMPVFQSLEAYWPGLOSLIGDIDNAMRTFLNYYTVWKQFG  
GLPEFYNIPOGYTVEKREGYPLRPELIESAMYLYRATGDPTLLELGRDAVESIEKISKVECG  
FATIKDLRDHKLDNRMESFFLAETVKYLYLLFDPTNFIHNNGSTFDAVITPYGECILGAGGY  
IFNTEAHPIDLAALHCCQRLKEEQWEVEDLMREFYSLKRSRSKFQKNTVSSGPWEPPARPGT  
LFSPENHDQARERKPAKQKVPLLSCPSQPFTSKLALLGQVFLDSS

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**FIGURE 116**

AAAGTTACATTTTCTCTGGAAGTCTCCTAGGCCACTCCCTGCTGATGCAACATCTGGGTTTG  
GGCAGAAAGGAGGGTGCTTCGGAGCCCGCCCTTTCTGAGCTTCCTGGGCCGGCTCTAGAACA  
ATTCAGGCTTCGCTGCGACTCAGACCTCAGCTCCAACATATGCATTCTGAAGAAAGATGGCT  
GAGATGGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCAAAGTCTGAGTCTACCA  
AATGCAGACTTTCACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTCATGTGGTTTTTCT  
ACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGCCTGCCCCCTCAGAACCTC  
TCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTGATCGCGCCTGGAGA  
AACAGTGTACTATTCTGTGAATACCAGGGGGAGTACGAGAGCCTGTACACGAGCCACATCT  
GGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGTGATGTCACTGATGACATC  
ACGGCCACTGTGCCATACAACCTTCGTGTCAGGGCCACATTGGGCTCACAGACCTCAGCCTG  
GAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATCCTTACCCGACCTGGGATGGAGA  
TCACCAAAGATGGCTTCCACCTGGTTATTGAGCTGGAGGACCTGGGGCCCCAGTTTGAGTTC  
CTTGTGGCCTACTGGAGGAGGGAGCCTGGTGCCGAGGAACATGTCAAATGGTGAGGAGTGG  
GGGTATTCCAGTGCACCTAGAAACCATGGAGCCAGGGGCTGCATACTGTGTGAAGGCCCAGA  
CATTCGTGAAGGCCATTGGGAGGTACAGCGCCTTCAGCCAGACAGAATGTGTGGAGGTGCAA  
GGAGAGGCCATTCCCCTGGTACTGGCCCTGTTTGCCTTTGTTGGCTTCATGCTGATCCTTGT  
GGTCGTGCCACTGTTCGTCTGGAAAATGGGCCGGCTGCTCCAGTACTCCTGTTGCCCCGTGG  
TGGTCCTCCCAGACACCTTGAAAATAACCAATTCACCCCAGAAGTTAATCAGCTGCAGAAGG  
GAGGAGGTGGATGCCTGTGCCACGGCTGTGATGTCTCCTGAGGAACTCCTCAGGGCCTGGAT  
CTCATAGGTTTGCGGAAGGGCCCAGGTGAAGCCGAGAACCTGGTCTGCATGACATGGAAACC  
ATGAGGGGACAAGTTGTGTTTCTGTTTTCCGCCACGGACAAGGGATGAGAGAAGTAGGAAGA  
GCCTGTTGTCTACAAGTCTAGAAGCAACCATCAGAGGCAGGGTGGTTTGTCTAACAGAACAC  
TGACTGAGGCTTAGGGGATGTGACCTCTAGACTGGGGGCTGCCACTTGCTGGCTGAGCAACC  
CTGGGAAAAGTGACTTCATCCCTTCGGTCCTAAGTTTTCTCATCTGTAATGGGGGAATTACC  
TACACACCTGCTAAACACACACACACAGAGTCTCTCTCTATATATACACACGTACACATAAA  
TACACCCAGCACTTGCAAGGCTAGAGGGAAACTGGTGACACTCTACAGTCTGACTGATTGAG  
TGTTTCTGGAGAGCAGGACATAAATGTATGATGAGAATGATCAAGGACTCTACACACTGGGT  
GGCTTGGAGAGCCCACTTTCCCAGAATAATCCTTGAGAGAAAAGGAATCATGGGAGCAATGG  
TGTTGAGTTCACTTCAAGCCCAATGCCGGTGCAGAGGGGAATGGCTTAGCGAGCTCTACAGT  
AGGTGACCTGGAGGAAGGTCACAGCCACACTGAAAATGGGATGTGCATGAACACGGAGGATC  
CATGAACTACTGTAAAGTGTTGACAGTGTGTGCACACTGCAGACAGCAGGTGAAATGTATGT  
GTGCAATGCGACGAGAATGCAGAAGTCAGTAACATGTGCATGTTTGTGTGCTCCTTTTTTC  
TGTTGGTAAAGTACAGAATTCAGCAAATAAAAAGGGCCACCCTGGCCAAAAGCGGTAAAAAA  
AAAAA

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**FIGURE 117**

MQTFTMVLEEIWTSLEFMWFFYALIPCLLTDEVAILPAPQNLSVLSTNMKHLLMWSPVIAPE  
TVYYSVEYQGEYESLYTSHIWIPSSWCSLTEGPECDVTDDITATVPYNLRVRATLGSQTS  
SILKHPFNRNSTILTRPGMEITKDGFHLVIELEDLGPOFEFLVAYWRREPGAEEHVKMVRSG  
GIPVHLETMEPGAAYCVKAQTFVKAIGRYSAFSQTECVEVQGEAIPVLALFAFVGFMILV  
VVPLFVWKMGRLLQYSCCPVVLPDTLKITNSPQKLISCRREEVDACATAVMSPEELLRAWIS

**Important features:****Signal peptide:**

amino acids 1-29

**Transmembrane domain:**

amino acids 230-255

**N-glycosylation sites.**

amino acids 40-43 and 134-137

**Tissue factor proteins homology.**

amino acids 92-119

**Integrins alpha chain protein homology.**

amino acids 232-262



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**FIGURE 118**

TCCTGCTGATGCACATCTGGGTTTGGCAAAGGAGGTTGCTTCGAGCCGCCCTTTCTAGCTT  
CCTGGCCGGCTCTAGAACAATTCAGGCTTCGCTGCGACTAGACCTCAGCTCCAACATATGCA  
TTCTGAAGAAAGATGGCTGAGATGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGG  
TCAAACCTGAGTCTACCAAATGCAGACTTTCACAATGGTTCTAGAAGAAATCTGGACAAGTCT  
TTTCATGTGGTTTTTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGC  
CTGCCCCCTCAGAACCTCTCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCA  
GTGATCGCGCCTGGAGAAACAGTGTACTATTCTGTCTGAATACCAGGGGGAGTACGAGAGCCT  
GTACACGAGCCACATCTGGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGTG  
ATGTCACTGATGACATCACGGCCACTGTGCCATACAACCTTTGTGTCTAGGGCCACATTGGGC  
TCACAGACCTCAGCCTGGAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATCCTTAC  
CCGACCTGGGATGGAGATCACCAGAGATGGCTTNCACCTGGTTATTGAGCTGGAGGACCTGG  
GGCCCCAGTTTGAGTTCCTTGTGGCCTANTGGAGGAGGGGGCGAACCCCTTGCGGCGCAAGGG  
GTTNGCGAACCCCTTGCGGCCGCTGGGGTATCTCTCGAGAAAAGAGAGGCCCAATATGACCCAC  
ATACTCAATATGGACGAANTGCTATTGTCCACCTGTTTGAGTGGCGCTGGGTTGAT

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**FIGURE 119**

CGGACGCGTGGGCGCCACCTCCGGAACAAGCCATGGTGGCGGCGACGGTGGCAGCGGCGTG  
GCTGCTCCTGTGGGCTGCGGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAGGCGG  
TCAACATCCGGGGCAAACCTGGTGTGCTGGAGAAGTACCGCGGATCGGTGTCCCTGGTGGTG  
AATGTGGCCAGCGAGTGCGGCTTCACAGACCAGCACTACCGAGCCCTGCAGCAGCTGCAGCG  
AGACCTGGGCCCCCACCACCTTTAACGTGCTCGCCTTCCCCTGCAACCAGTTTGGCCAACAGG  
AGCCTGACAGCAACAAGGAGATTGAGAGCTTTGCCCCGCCGCACCTACAGTGTCTCATTCCCC  
ATGTTTAGCAAGATTGCAGTCACCGGTACTGGTGCCCATCCTGCCTTCAAGTACCTGGCCCA  
GACTTCTGGGAAGGAGCCACCTGGAACCTTCTGGAAGTACCTAGTAGCCCCAGATGGAAAGG  
TGGTAGGGGCTTGGGACCCAACTGTGTCAGTGGAGGAGGTCAGACCCCAGATCACAGCGCTC  
GTGAGGAAGCTCATCCTACTGAAGCGAGAAGACTTATAACCACCGCGTCTCCTCCTCCACCA  
CCTCATCCCGCCACCTGTGTGGGGCTGACCAATGCAAACCTCAAATGGTGCTTCAAAGGGAG  
AGACCCACTGACTCTCCTTCCTTTACTCTTATGCCATTGGTCCCATCATTCTTGTGGGGGAA  
AAATTCTAGTATTTTGATTATTTGAATCTTACAGCAACAAATAGGAACTCCTGGCCAATGAG  
AGCTCTTGACCAGTGAATCACCAGCCGATACGAACGTCTTGCCAACAAAAATGTGTGGCAAA  
TAGAAGTATATCAAGCAATAATCTCCCACCCAAGGCTTCTGTAAACTGGGACCAATGATTAC  
CTCATAGGGCTGTTGTGAGGATTAGGATGAAATACCTGTGAAAGTGCCTAGGCAGTGCCAGC  
CAAATAGGAGGCATTCAATGAACATTTTTTGCATATAAACCAAAAAATAACTTGTTATCAAT  
AAAAACTTGCATCCAACATGAATTTCCAGCCGATGATAATCCAGGCCAAAGGTTTAGTTGTT  
GTTATTTCTCTGTATTATTTTCTTCATTACAAAAGAAATGCAAGTTCATTGTAACAATCCA  
ACAATACCTCACGATATAAAATAAAAAATGAAAGTATCCTCCTCAAAAA

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**FIGURE 120**

MVAATVAAAWLLLWAAACAQQEQDFYDFKAVNIRGKLVSLEKYRGSVSLVVNVASECGFTDQ  
HYRALQQQLQRDLGPHHFNVLAFFPCNQFGQQEPDSNKEIESFARRTYSVSFPMFSKIAVTGTG  
AHPAFKYLAQTSGKEPTWNFWKYL VAPDGKVVGAWDPTVSVEEVRPQITALVRKLILLKREDL

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**FIGURE 121**

CGGACGCGTGGGCGGGCCGGGACGCAGGGCAAAGCGAGCCATGGCTGTCTACGTCGGGATGC  
TGCGCCTGGGGAGGCTGTGCGCCGGGAGCTCGGGGGTGCTGGGGGCCCGGGCCGCCCTCTCT  
CGGAGTTGGCAGGAAGCCAGGTTGCAGGGTGTCCGCTTCCTCAGTTCCAGAGAGGTGGATCG  
CATGGTCTCCACGCCCATCGGAGGCCTCAGCTACGTTCAAGGGGTGCACCAAAAAGCATCTTA  
ACAGCAAGACTGTGGGCCAGTGCCTGGAGACCACAGCACAGAGGGTCCCAGAACGAGAGGCC  
TTGGTCGTCCTCCATGAAGACGTCAGGTTGACCTTTGCCCAACTCAAGGAGGAGGTGGACAA  
AGCTGCTTCTGGCCTCCTGAGCATTTGGCCTCTGCAAAGGTGACCGGCTGGGCATGTGGGGAC  
CTAACTCCTATGCATGGGTGCTCATGCAGTTGGCCACCGCCCAGGCGGGCATCATTCTGGTG  
TCTGTGAACCCAGCCTACCAGGCTATGGAAGTGGAGTATGTCCTCAAGAAGGTGGGCTGCAA  
GGCCCTTGTGTTCCCCAAGCAATTCAAGACCCAGCAATACTACAACGTCTTGAAGCAGATCT  
GTCCAGAAGTGGAGAATGCCAGCCAGGGGCTTGAAGAGTCAGAGGCTCCCAGATCTGACC  
ACAGTCATCTCGGTGGATGCCCCCTTTGCCGGGGACCTGCTCCTGGATGAAGTGGTGGCGGC  
TGGCAGCACACGGCAGCATCTGGACCAGCTCCAATACAACCAGCAGTTCCTGTCCTGCCATG  
ACCCCATCAACATCCAGTTCACCTCGGGGACAACAGGCAGCCCCAAGGGGGGCCACCTCTCC  
CACTACAACATTGTCAACAACCTCCAACATTTTAGGAGAGCGCCTGAAACTGCATGAGAAGAC  
ACCAGAGCAGTTGCGGATGATCCTGCCCAACCCCTGTACCATTGCCTGGGTTCGCTGGCAG  
GCACAATGATGTGTCTGATGTACGGTGCCACCCTCATCCTGGCCTCTCCCATCTTCAATGGC  
AAGAAGGCACTGGAGGCCATCAGCAGAGAGAGAGGCACCTTCCTGTATGGTACCCCCACGAT  
GTTCTGTTGCTGGGTCCCCTGCACCTCCAGAGTTGATCCGAGCCATCATCAACAAGATAAAT  
ATGAAGGACCTGGTGGTTGCTTATGGAACCACAGAGAACAGTCCCGTGACATTCGCGCACTT  
CCCTGAGGACACTGTGGAGCAGAAGGCAGAAAGCGTGGGCAGAATTATGCCTCACACGGAGG  
CCCGGATCATGAACATGGAGGCAGGGACGCTGGCAAAGCTGAACACGCCCCGGGGAGCTGTGC  
ATCCGAGGGTACTGCGTCATGCTGGGCTACTGGGGTGAGCCTCAGAAGACAGAGGAAGCAGT  
GGATCAGGACAAGTGGTATTGGACAGGAGATGTCGCCACAATGAATGAGCAGGGCTTCTGCA  
AGATCGTGGGCCGCTCTAAGGATATGATCATCCGGGGTGGTGAGAACATCTACCCCGCAGAG  
CTCGAGGACTTCTTTACACACACCCGAAGGTGCAGGAAGTGCAGGTGGTGGGAGTGAAGGA  
CGATCGGATGGGGGAAGAGATTTGTGCCTGCATTTCGGCTGAAGGACGGGGAGGAGACCACGG  
TGGAGGAGATAAAAGCTTTCTGCAAAGGGAAGATCTCTCACTTCAAGATTCCGAAGTACATC  
GTGTTTGTCAAACTACCCCTCACCATTTTCAGGAAAGATCCAGAAATTCAAACCTTCGAGA  
GCAGATGGAACGACATCTAAATCTGTGAATAAAGCAGCAGGCCTGTCCTGGCCGGTTGGCTT  
GACTCTCTCCTGTCAGAATGCAACCTGGCTTTATGCACCTAGATGTCCCCAGCACCCAGTTC  
TGAGCCAGGCACATCAAATGTCAAGGAATTGACTGAACGAACTAAGAGCTCCTGGATGGGTC  
CGGGAACCTCGCCTGGGCACAAGGTGCCAAAAGGCAGGCAGCCTGCCAGGCCCTCCCTCCTG  
TCCATCCCCCACATTCCCCTGTCTGTCCTTGTGATTTGGCATAAAGAGCTTCTGTTTTCTTT  
GAAAAAAAAAAAAAAAAA



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**FIGURE 122**

MAVYVGMLRLGRLCAGSSGVLGARAALSRWQEARLQGVRFLLSSREVDRMVSTPIGGLSYVQ  
GCTKKHLNSKTVGQCLETTAQRVPEREALVVLHEDVRLTFAQLKEEVDKAASGLLSIGLCKG  
DRLGMWGPNSYAWVLMQLATAQAGIILVSVNPAYQAMELEYVLKKVGCKALVFPKQFKTQQY  
YNVLKQICPEVENAQPGLKSQRLPDLTTVISVDAPLPGTLLLDEVVAAGSTRQHLDQLQYN  
QQFLSCHDPINIQFTSGTTGSPKGATLSHYNIVNNSNILGERLKLHEKTPEQLRMILPNPLY  
HCLGSVAGTMMCLMYGATLILASPIFNGKKALEAISRERGTFLYGTPTMFVDILNQPDFSSY  
DISTMCGGVIAGSPAPPELIRAIINKINMKDLVVAYGTTENSPVTFAHFPEDTVEQKAESVG  
RIMPHTEARIMNMEAGTLAKLNTPGELCIRGYCVMLGYWGEPQKTEEAVDQDKWYWTGDVAT  
MNEQGFCKIVGRSKDMIIRGGENIYPAELEDFHTHPKVQEVQVVGVKDDRMGEEICACIRL  
KDGEETTVEEIKAFCKGKISHFKIPKYIVFVTNYPLTISGKIQKFKLREQMERHLNL

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**FIGURE 123**

CAACTCCAACATTTTAGGAGAGCGCCTGAAACTGCATGAGAAGACACCAGAGCAGTTGCGGA  
TGATCCTGCCCAACCCCCTGTACCATTGCCTGGGTTCCGTGGCAGGCACAATGATGTGTCTG  
ATGTACGGTGCCACCCTCATCCTGGCCTCTCCCATCTTCAATGGCAAGAAGGCACTGGAGGC  
CATCAGCAGAGAGAGAGAGGCACCTTCCTGTATGGTACCCCCACGATGTTTCGTGGACATTCTGA  
ACCAGCCAGACTTCTCCAGTTATGACATCTCGACCATGTGTGGAGGTGTCATTGCTGGGTCC  
CCTGCACCTCCAGAGTTGATCCGAGCCATCATCAACAAGATAAATATGAAGGACCTGGTGGT  
TGCTTATGGAACCACAGAGAACAGTCCCGTGACATTCGCGCACTTCCCTGAGGACACTGTGG  
AGCAGAAGGCAGAAAGCGTGGGCAGAATTATGCCTCACACGGAGGCGCGGATCATGAACATG  
GAGGCAGGGACGCTGGCAAAGCTGAACACGCCCGGGGAGCTGTGCATCCGAGGGTACTGCGT  
CATGCTGGGCTACTGGGGTGAGCCTCAGAAGACAGAGGAAGCAGTGGATCAGGACAAGTGGT  
ATTGGACAGGAGATGTCGCCAC

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**FIGURE 124**

GAGCAGGACGGAGCCATGGACCCCGCCAGGAAAGCAGGTGCCCAGGCCATGATCTGGACTGC  
AGGCTGGCTGCTGCTGCTGCTGCTTCGCGGAGGAGCGCAGGCCCTGGAGTGCTACAGCTGCG  
TGCAGAAAGCAGATGACGGATGCTCCCCGAACAAGATGAAGACAGTGAAGTGCGCGCCGGGC  
GTGGACGTCTGCACCGAGGCCGTGGGGGCGGTGGAGACCATCCACGGACAATTCTCGCTGGC  
AGTGCGGGGTTGCGGTTCTGGGACTCCCCGGCAAGAATGACCGCGGCCTGGATCTTCACGGGC  
TTCTGGCGTTCATCCAGCTGCAGCAATGCGCTCAGGATCGCTGCAACGCCAAGCTCAACCTC  
ACCTCGCGGGCGCTCGACCCGGCAGGTAATGAGAGTGCATACCCGCCCAACGGCGTGGAGTG  
CTACAGCTGTGTGGGCCTGAGCCGGGAGGCGTGCCAGGGTACATCGCCGCCGGTCTGTGAGCT  
GCTACAACGCCAGCGATCATGTCTACAAGGGCTGCTTCGACGGCAACGTCACCTTGACGGCA  
GCTAATGTGACTGTGTCCTTGCCCTGTCCGGGGCTGTGTCCAGGATGAATTCTGCACTCGGGA  
TGGAGTAACAGGCCCCAGGGTTCACGCTCAGTGGCTCCTGTTGCCAGGGGTCCCGCTGTAACT  
CTGACCTCCGCAACAAGACCTACTTCTCCCCTCGAATCCCACCCCTTGTCCGGCTGCCCCCT  
CCAGAGCCCACGACTGTGGCCTCAACCACATCTGTCACCACTTCTACCTCGGCCCCAGTGAG  
ACCCACATCCACCACCAAACCCATGCCAGCGCCAACCAGTCAGACTCCGAGACAGGGAGTAG  
AACACGAGGCCTCCCGGGATGAGGAGCCCAGGTTGACTGGAGGCGCCGCTGGCCACCAGGAC  
CGCAGCAATTCAGGGCAGTATCCTGCAAAAGGGGGGCCCCAGCAGCCCCATAATAAAGGCTG  
TGTGGCTCCACAGCTGGATTGGCAGCCCTTCTGTTGGCCGTGGCTGCTGGTGTCTACTGT  
GAGCTTCTCCACCTGGAAATTTCCCTCTCACCTACTTCTCTGGCCCTGGGTACCCCTCTTCT  
CATCACTTCTGTTCCCACTGACTGGGCTGGCCCAGCCCCTGTTTTTCCAACATTCCC  
CAGTATCCCCAGCTTCTGCTGCGCTGGTTTTCGGGCTTTGGGAAATAAAATACCGTTGTATAT  
ATTCTGCCAGGGGTGTTCTAGCTTTTTGAGGACAGCTCCTGTATCCTTCTCATCCTTGTCTC  
TCCGCTTGTCTCTTGTGATGTTAGGACAGAGTGAGAGAAGTCAGCTGTCACGGGGAAGGTG  
AGAGAGAGGATGCTAAGCTTCCTACTCACTTTCTCCTAGCCAGCCTGGACTTTGGAGCGTGG  
GGTGGGTGGGACAATGGCTCCCCACTCTAAGCACTGCCTCCCCTACTCCCCGCATCTTTGGG  
GAATCGGTTCCCATATGTCTTCCTTACTAGACTGTGAGCTCCTCGAGGGGGGGCCCGGTAC  
CCAATTCGCCCTATAGTGAGTCGTA

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**FIGURE 125**

MDPARKAGAQAMIWTAGWLLLLLLLRGGAQALECYSCVQKADDGCSPNKMKTVKCAPGVDVCT  
EAVGAVETIHGQFSLAVRGCGSGLPGKNDRGLDLHGLLAFIQLQQCAQDRCNALNLTSRAL  
DPAGNESAYPPNGVECYSCVGLSREACQGTSPPVVSCYNASDHVYKGCDFDGNVTLTAANVTV  
SLPVRGCVQDEFCTRDGVTGPGFTLSGSCCQGSRCNSDLRNKTYFSPRIPLVRLPPPEPTT  
VASTTSVTTSTSAPVRPTSTTKPMPAPTSQTPRQGEHEASRDEEPRLTGGAAGHQDRSNSG  
QYPAKGGPQQPHNKGCVAPTAGLAALLLAVAAGVLL



## FIGURE 126

CGGGACTCGGCGGGTCTCTCTGGGAGTCTCGGAGGGGACCGGCTGTGCAGACGCCATGGAGT  
TGGTGCTGGTCTTCCTCTGCAGCCTGCTGGCCCCCATGGTCCTGGCCAGTGCAGCTGAAAAG  
GAGAAGGAAATGGACCCCTTTTCATTATGATTACCAGACCCCTGAGGATTGGGGGACTGGTGTT  
CGCTGTGGTCCTCTTCTCGGTTGGGATCCTCCTTATCCTAAGTCGCAGGTGCAAGTGCAGTT  
TCAATCAGAAGCCCCGGGGCCCCAGGAGATGAGGAAGCCCAGGTGGAGAACCTCATCACCGCC  
AATGCAACAGAGCCCCAGAAGCAGAGAACTGAAGTGCAGCCATCAGGTGGAAGCCTCTGGAA  
CCTGAGGCGGCTGCTTGAACCTTTGGATGCAAATGTCGATGCTTAAGAAAAACCGGCCACTTC  
AGCAACAGCCCTTTCCCCAGGAGAAGCCAAGAAGTGTGTGTCCCCCACCCTATCCCCTCTA  
ACACCATTCTCCACCTGATGATGCAACTAACACTTGCCTCCCCACTGCAGCCTGCGGTCCT  
GCCACCTCCCGTGATGTGTGTGTGTGTGTGTGTGTGTGACTGTGTGTGTTTGCTAACTGTG  
GTCTTTGTGGCTACTTGTTTGTGGATGGTATTGTGTTTGTTAGTGAAGTGTGGACTCGCTTT  
CCCAGGCAGGGGCTGAGCCACATGGCCATCTGCTCCTCCCTGCCCCCGTGGCCCTCCATCAC  
CTTCTGCTCCTAGGAGGCTGCTTGTTGCCCGAGACCAGCCCCCTCCCCTGATTTAGGGATGC  
GTAGGGTAAGAGCACGGGCAGTGGTCTTCAGTCGTCTTGGGACCTGGGAAGGTTTGCAGCAC  
TTTGTTCATCATTCTTCATGGACTCCTTTCACTCCTTTAACAAAAACCTTGCTTCCTTATCCC  
ACCTGATCCCAGTCTGAAGGTCTCTTAGCAACTGGAGATACAAAGCAAGGAGCTGGTGAGCC  
CAGCGTTGACGTCAGGCAGGCTATGCCCTTCCGTGGTTAATTTCTTCCCAGGGGGCTTCCACG  
AGGAGTCCCCATCTGCCCCGCCCCCTTCACAGAGCGCCCGGGGATTCCAGGCCCAGGGCTTCT  
ACTCTGCCCCCTGGGGGAATGTGTCCCCTGCATATCTTCTCAGCAATAACTCCATGGGCTCTGG  
GACCCTACCCCTTCCAACCTTCCCTGCTTCTGAGACTTCAATCTACAGCCCAGCTCATCCAG  
ATGCAGACTACAGTCCCTGCAATTGGGTCTCTGGCAGGCAATAGTTGAAGGACTCCTGTTCC  
GTTGGGGGCCAGCACACCGGGATGGATGGAGGGAGAGCAGAGGCCTTTGCTTCTCTGCCTACG  
TCCCCTTAGATGGGCAGCAGAGGCAACTCCCGCATCCTTTGCTCTGCCTGTCGGTGGTCAGA  
GCGGTGAGCGAGGTGGGTTGGAGACTCAGCAGGCTCCGTGCAGCCCTTGGGAACAGTGAGAG  
GTTGAAGGTCATAACGAGAGTGGGAAGTCAACCCAGATCCCGCCCCCTCCTGTCCTCTGTGTT  
CCCGCGGAAACCAACCAAACCGTGCGCTGTGACCCATTGCTGTTCTCTGTATCGTGATCTAT  
CCTCAACAACAACAGAAAAAAGGAATAAAATATCCTTTGTTTCCT

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**FIGURE 127**

MELVLVFLCSLLAPMVLASAAEKEKEMDPFHYDYQTLRIGGLVFAVVLFSVGILLILSRCK  
CSFNQKPRAPGDEEAQVENLITANATEPQKQORTEVQPSGGSLWNLRRLLLEPLDANVDA

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**FIGURE 128**

AAACTTGACGCCATGAAGATCCCGGTCCTTCCTGCCGTGGTGCTCCTCTCCCTCCTGGTGCT  
CCTCTGCCCAGGGAGCCACCCTGGGTGGTCCTGAGGAAGAAAGCACCATTTGAGAATTATG  
CGTCACGACCCGAGGCCTTTAACACCCCGTTCCTGAACATCGACAAATTGCGATCTGCGTTT  
AAGGCTGATGAGTTCCTGAACTGGCACGCCCTCTTTGAGTCTATCAAAAGGAACTTCCTTT  
CCTCAACTGGGATGCCTTTCCTAAGCTGAAAGGACTGAGGAGCGCAACTCCTGATGCCCAGT  
GACCATGACCTCCACTGGAAGAGGGGGCTAGCGTGAGCGCTGATTCTCAACCTACCATAACT  
CTTTCCTGCCTCAGGAACTCCAATAAAACATTTTCCATCCAAA

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**FIGURE 129**

MKIPVLPVVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSFAKDE  
FLNWHALFESIKRKLPFLNWDAFPKLGKGLRSATPDAQ



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**FIGURE 130**

CAGTTCTGAAATCAATGGAGTTAATTTAGGGAATACAAACCAGCCATGGGGGTGGAGATTGC  
CTTTGCCTCAGTGATTCTCACCTGCCTCTCCCTTCTGGCAGCAGGAGTCTCCCAGGTTGTTT  
TTCTCCAGCCAGTTCCAACCTCAGGAGACAGGTCCCAAGGCCATGGGAGATCTCTCCTGTGGC  
TTTGCCGGCCACTCATGAGAGTGTTTTTGTGTAAAGTATTTTTTTAGAATACTGTTGACTTCT  
TCATGATTTAATAACCATCCTTTGCGAAGTTTTATGAGGCTTTAGGGGAATGTCAACCCTCA  
AATTTTTGTTATACTAGATGGCTTCCATTTACCCACCACTATTTTAAGGTCCCTTTATTTTT  
AGGTTCAAGGTTCAATTTGACTTGAGAAAGTGCCCTTCTGCAGCTTCATTGATTTTGTTTATC  
TTCACCTATTAATTGTAACGATTAAAAAGAATAAGAGCACGCAGACCTCTAGGAGAATATTT  
TATCCCTGGGTGCCCCTGACACATTTATGTAGTGATCCCACAAATGTGATTGTTAATTTAAA  
TGTTATTCTAATATTAGTACATTCAGTTGTGATGTAATATGAATAACCAGAATCTATTTCTT  
AAAAGTTTTGAGTATATTTTTTCAACTAGATATTTGTATAGAAAGACTGAATAGTGATG

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**FIGURE 131**

MGVEIAFASVILTCLSLAAGVSQVLLQPVPTQETGPKAMGDLSCGFAGHS

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**FIGURE 132**

GGGGAATCTGCAGTAGGTCTGCCGGCGATGGAGTGGTGGGCTAGCTCGCCGCTTCGGCTCTG  
GCTGCTGTTGTTCTCCTGCCCTCAGCGCAGGGCCGCCAGAAGGAGTCAGGTTCAAAATGGA  
AAGTATTTATTGACCAAATTAACAGGTCTTTGGAGAATTACGAACCATGTTCAAGTCAAAAC  
TGCAGCTGCTACCATGGTGT CATAGAAGAGGATCTAACTCCTTTCCGAGGAGGCATCTCCAG  
GAAGATGATGGCAGAGGTAGTCAGACGGAAGCTAGGGACCCACTATCAGATCACTAAGAACA  
GACTGTACCGGGAAAATGACTGCATGTTCCCCTCAAGGTGTAGTGGTGTGAGCACTTTATT  
TTGGAAGTGATCGGGCGTCTCCCTGACATGGAGATGGTGATCAATGTACGAGATTATCCTCA  
GGTTCCTAAATGGATGGAGCCTGCCATCCCAGTCTTCTCCTTCAGTAAGACATCAGAGTACC  
ATGATATCATGTATCCTGCTTGGACATTTTGGGAAGGGGGACCTGCTGTTTGGCCAATTTAT  
CCTACAGGTCTTGGACGGTGGGACCTCTTCAGAGAAGATCTGGTAAGGTCAGCAGCACAGTG  
GCCATGGAAAAAGAAAACTCTACAGCATATTTCCGAGGATCAAGGACAAGTCCAGAACGAG  
ATCCTCTCATTCTTCTGTCTCGGAAAAACCCAAAACCTTGTTGATGCAGAATACACCAAAAAC  
CAGGCCTGGAAATCTATGAAAGATACCTTAGGAAAGCCAGCTGCTAAGGATGTCCATCTTGT  
GGATCACTGCAAATACAAGTATCTGTTTAATTTTCGAGGCGTAGCTGCAAGTTTCCGGTTTA  
AACACCTCTTCCTGTGTGGCTCACTTGTTTTCCATGTTGGTGATGAGTGGCTAGAATTCTTC  
TATCCACAGCTGAAGCCATGGGTTCCTATATCCCAGTCAAAACAGATCTCTCCAATGTCCA  
AGAGCTGTTACAATTTGTAAAAGCAAATGATGATGTAGCTCAAGAGATTGCTGAAAGGGGAA  
GCCAGTTTATTAGGAACCATTTGCAGATGGATGACATCACCTGTTACTGGGAGAACCTCTTG  
AGTGAATACTCTAAATTCCTGTCTTATAATGTAACGAGAAGGAAAGGTTATGATCAAATTAT  
TCCCAAAATGTTGAAAACCTGAACTATAGTAGTCATCATAGGACCATAGTCCTCTTTGTGGCA  
ACAGATCTCAGATATCCTACGGTGAGAAGCTTACCATAAGCTTGGCTCCTATACCTTGAATA  
TCTGCTATCAAGCCAAATACCTGGTTTTCTTATCATGCTGCACCCAGAGCAACTCTTGAGA  
AAGATTTAAAATGTGTCTAATACTGATATGAAGCAGTTCAACTTTTTGGATGAATAAGGA  
CCAGAAATCGTGAGATGTGGATTTTGAACCCAACTCTACCTTTCATTTTCTTAAGACCAATC  
ACAGCTTGTCCTCAGATCATCCACCTGTGTGAGTCCATCACTGTGAAATTGACTGTGTCCA  
TGTGATGATGCCCTTTGTCCCATTTTGGAGCAGAAAATTCGTCATTTGGAAGTAGTACAA  
CTCATTGCTGGAATTGTGAAATTATTCAAGGCGTGATCTCTGTCACTTTATTTTAATGTAGG  
AAACCTTATGGGGTTTATGAAAAATACTTGGGGATCATTCTCTGAATGGTCTAAGGAAGCGG  
TAGCCATGCCATGCAATGATGTAGGAGTTCTCTTTTGTAAAACCATAAACTCTGTTACTCAG  
GAGGTTTCTATAATGCCACATAGAAAGAGGCCAATTGCATGAGTAATTATTGCAATTGGATT  
TCAGGTTCCCTTTTTGTGCCTTCATGCCCTACTTCTTAATGCCTCTCTAAAGCCAAA

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**FIGURE 133**

MEWWASSPLRLWLLLFLLP  
SAQGRQKESGSKWKVFIDQ  
INRSLENYEPCSSQNCSCY  
HGVIE  
EDLTPFRGGISRKMMAEV  
VRRKLGTHYQITKNRLYRE  
NDCMFPSRCSGVEHFILEV  
IGRLPD  
MEMVINVRDYPQVPKWME  
PAIPVFSFSKTSEYHDIMY  
PAWTFWEGGPAVWPIYPTG  
LGRWDL  
FREDLVRSAAQWPWKKKN  
STAYFRGSRTSPERDPLIL  
LSRKNPKLVDAEYTKNQAW  
KSMKDT  
LGKPAAKDVHLVDHCKYK  
YLFNFRGVAASFRFKHLFL  
CGSLVFHVGDEWLEFFYPQ  
LKPVH  
YIPVKTDLSNVQELLQFV  
KANDDVAQEIAERGSQFIR  
NHLQMDDITCYWENLLSEY  
SKFLSY  
NVTRRKGYDQIIPKMLK  
TEL



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**FIGURE 134**

CACCCCTCCATTTCTCGCCATGGCCCCTGCACTGCTCCTGATCCCTGCTGCCCTCGCCTCTT  
TCATCCTGGCCTTTGGCACCGGAGTGGAGTTCGTGCGCTTTACCTCCCTTCGGCCACTTCTT  
GGAGGGATCCCGGAGTCTGGTGGTCCGGATGCCCCGCCAGGGATGGCTGGCTGCCCTGCAGGA  
CCGCAGCATCCTTGCCCCCCTGGCATGGGATCTGGGGCTCCTGCTTCTATTTGTTGGGCAGC  
ACAGCCTCATGGCAGCTGAAAGAGTGAAGGCATGGACATCCCGGTACTTTGGGGTCCTTCAG  
AGGTCACCTGTATGTGGCCTGCACTGCCCTGGCCTTGCAGCTGGTGATGCGGTACTGGGAGCC  
CATACCCAAAGGCCCTGTGTTGTGGGAGGCTCGGGCTGAGCCATGGGGCCACCTGGGTGCCGC  
TCCTCTGCTTTGTGCTCCATGTCATCTCCTGGCTCCTCATCTTTAGCATCCTTCTCGTCTTT  
GACTATGCTGAGCTCATGGGCCTCAAACAGGTATACTACCATGTGCTGGGGCTGGGCGAGCC  
TCTGGCCCTGAAGTCTCCCCGGGCTCTCAGACTCTTCTCCACCTGCGCCACCCAGTGTGTG  
TGGAGCTGCTGACAGTGCTGTGGGTGGTGCCTACCCTGGGCACGGACCGTCTCCTCCTTGCT  
TTCCTCCTTACCCTCTACCTGGGCCTGGCTCACGGGCTTGATCAGCAAGACCTCCGCTACCT  
CCGGGCCCAGCTACAAAGAAAACCTCCACCTGCTCTCTCGGCCCCAGGATGGGGAGGCAGAGT  
GAGGAGCTCACTCTGGTTACAAGCCCTGTTCTTCCTCTCCCACTGAATTCTAAATCCTTAAC  
ATCCAGGCCCTGGCTGCTTCATGCCAGAGGCCCAAATCCATGGACTGAAGGAGATGCCCCTT  
CTACTACTTGAGACTTTATTCTCTGGGTCCAGCTCCATACCCTAAATTCTGAGTTTCAGCCA  
CTGAACTCCAAGGTCCACTTCTCACCAGCAAGGAAGAGTGGGGTATGGAAGTCATCTGTCCC  
TTCACCTGTTTAGAGCATGACACTCTCCCCCTCAACAGCCTCCTGAGAAGGAAAGGATCTGCC  
CTGACCACTCCCCTGGCACTGTTACTTGCCTCTGCGCCTCAGGGGTCCCCTTCTGCACCGCT  
GGCTTCCACTCCAAGAAGGTGGACCAGGGTCTGCAAGTTCAACGGTCATAGCTGTCCCTCCA  
GGCCCCAACCTTGCCTCACCCTCCCGGCCCTAGTCTCTGCACCTCCTTAGGCCCTGCCTCT  
GGGCTCAGACCCCAACCTAGTCAAGGGGATTCTCCTGCTCTTAACTCGATGACTTGGGGCTC  
CCTGCTCTCCCGAGGAAGATGCTCTGCAGGAAAATAAAAGTCAGCCTTTTTCTAAAAAAA

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**FIGURE 135**

MAPALLLI PAALASFILAFGTGVEFVRFTSLRPLLGGIPESGGPDARQGWLAALQDRSILAP  
LAWDLGLLLLLFVGQHSILMAAERVKAWSRYFGVLQRSLYVACTALALQLVMRYWEPIPKGPV  
LWEARAEPWATWVPLLCFVLHVISWLLIFSILLVFDYAELMGLKQVYYHVLGLGEPLALKSP  
RALRLFSHLRHPVCVELLTVLWVVPTLGTDRLLLAFLLTLYLGLAHGLDQQDLRYLRAQLQR  
KLHLLSRPQDGEAE

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**FIGURE 136**

CCGAGCACAGGAGATTGCCTGCGTTTAGGAGGTGGCTGCGTTGTGGGAAAAGCTATCAAGGA  
AGAAATTGCCAAACCATGTCTTTTTTTCTGTTTTTCAGAGTAGTTTACAACAGATCTGAGTGT  
TTTAATTAAGCATGGAATACAGAAAACAACAAAAAACTTAAGCTTTAATTTTCATCTGGAATT  
CCACAGTTTTCTTAGCTCCCTGGACCCGGTTGACCTGTTGGCTCTTCCCGCTGGCTGCTCTA  
TCACGTGGTGCTCTCCGACTACTCACCCCGAGTGTAAGAACCTTCGGCTCGCGTGCTTCTG  
AGCTGCTGTGGATGGCCTCGGCTCTCTGGACTGTCCTTCCGAGTAGGATGTCACTGAGATCC  
CTCAAATGGAGCCTCCTGCTGCTGTCACCTCCTGAGTTTCTTTGTGATGTGGTACCTCAGCCT  
TCCCCACTACAATGTGATAGAACGCGTGAACCTGGATGTACTTCTATGAGTATGAGCCGATTT  
ACAGACAAGACTTTCACTTCACACTTCGAGAGCATTCAAACCTGCTCTCATCAAAATCCATTT  
CTGGTCATTCTGGTGACCTCCCACCCTTCAGATGTGAAAGCCAGGCAGGCCATTAGAGTTAC  
TTGGGGTGAAAAAAAGTCTTGGTGGGGATATGAGGTTCTTACATTTTTCTTATTAGGCCAAG  
AGGCTGAAAAGGAAGACAAAATGTTGGCATTGTCCTTAGAGGATGAACACCTTCTTTATGGT  
GACATAATCCGACAAGATTTTTTTAGACACATATAATAACCTGACCTTGAAAACCATTTATGGC  
ATTCAGGTGGGTAACTGAGTTTTGCCCCAATGCCAAGTACGTAATGAAGACAGACACTGATG  
TTTTTCATCAATACTGGCAATTTAGTGAAGTATCTTTTAAACCTAAACCACTCAGAGAAGTTT  
TTCACAGGTTATCCTCTAATTGATAATTATTCCTATAGAGGATTTTACCAAAAAACCCATAT  
TTCTTACCAGGAGTATCCTTTCAAGGTGTTCCCTCCATACTGCAGTGGGTGGGTATATATAA  
TGTCCAGAGATTTGGTGCCAAGGATCTATGAAATGATGGGTACGTAAAACCCATCAAGTTT  
GAAGATGTTTATGTCGGGATCTGTTTGAATTTATTAAAAGTGAACATTCATATTCCAGAAGA  
CACAAATCTTTTCTTTCTATATAGAATCCATTTGGATGTCTGTCAACTGAGACGTGTGATTG  
CAGCCCATGGCTTTTCTTCCAAGGAGATCATCACTTTTTTGGCAGGTCATGCTAAGGAACACC  
ACATGCCATTATTAACTTCACATTCTACAAAAAGCCTAGAAGGACAGGATACCTTGTGGAAA  
GTGTTAAATAAAGTAGGTACTGTGGAAAATTCATGGGGAGGTGAGTGTGCTGGCTTACACTG  
AACTGAAACTCATGAAAAACCCAGACTGGAGACTGGAGGGTTACACTTGTGATTTATTAGTC  
AGGCCCTTCAAAGATGATATGTGGAGGAATTAAATATAAAGGAATTGGAGGTTTTTGCTAAA  
GAAATTAATAGGACCAAACAATTTGGACATGTCATTCTGTAGACTAGAATTTCTTAAAAGGG  
TGTTACTGAGTTATAAGCTCACTAGGCTGTAAAAACAAAACAATGTAGAGTTTTTATTTATTG  
AACAATGTAGTCACTTGAAGGTTTTGTGTATATCTTATGTGGATTACCAATTTAAAAATATA  
TGTAAGTTCTGTGTCAAAAAAATTTCTTCACTGAAGTTATACTGAACAAAATTTTACCTGTTTT  
TGGTCATTTATAAAGTACTTCAAGATGTTGCAGTATTTACAGTTATTATTATTATAAATTA  
CTTCAACTTTGTGTTTTTAAATGTTTTGACGATTTCAATACAAGATAAAAAGGATAGTGAAT  
CATTCTTTACATGCAAACATTTTCCAGTTACTTAACTGATCAGTTTATTATTGATACATCAC  
TCCATTAATGTAAAGTCATAGGTCATTATTGCATATCAGTAATCTCTTGGACTTTGTAAAT  
ATTTTACTGTGGTAATATAGAGAAGAATTAAAGCAAGAAAATCTGAAAA

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**FIGURE 137**

MASALWTVLPSRMSLRSLKWSLLLLSLLSFFVMWYLSLPHYNVIERVNWMYFYEYEPYRQD  
FHFTLREHSNCSHQNPFLVILVTSHPSDVKARQAIRVTWGEKKSWWGYEVLTFLLGQEA EK  
EDKMLALSLEDEHLLYGDII RQDFLDTYNNLT LKTIMAFRWVTEFCPNAKYVMKTD TDVF IN  
TGNLVKYLLNLNHSEKFFTGYPLIDNYSYRGFYQKTHISYQEYPFKVFPPYCSGLGYIMSRD  
LVPRIYEMMGHV KPIKFEDVYVGICLNLLKVNIHIPEDTNLFFLYRIHLDVCQLRRVIAAHG  
FSSKEIITFWQVMLRNTTCHY



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**FIGURE 138**

CCTCTGTCCACTGCTTTCGTGAAGACAAGATGAAGTCACAATTGTCTTTGCTGGACTTCTT  
GGAGTCTTTCTAGCTCCTGCCCTAGCTAACTATAATATCAACGTCAATGATGACAACAACAA  
TGCTGGAAGTGGGCAGCAGTCAGTGAGTGTCAACAATGAACACAATGTGGCCAATGTTGACA  
ATAACAACGGATGGGACTCCTGGAATTCCATCTGGGATTATGGAAATGGCTTTGCTGCAACC  
AGACTCTTTCAAAGAAGACATGCATTGTGCACAAAATGAACAAGGAAGTCATGCCCTCCAT  
TCAATCCCTTGATGCACTGGTCAAGGAAAAGAAGCTTCAGGGTAAGGGACCAGGAGGACCAC  
CTCCCAAGGGCCTGATGTACTCAGTCAACCCAAACAAAGTCGATGACCTGAGCAAGTTCGGA  
AAAAACATTGCAAACATGTGTCTGTGGGATTCCAACATACATGGCTGAGGAGATGCAAGAGGC  
AAGCCTGTTTTTTTACTCAGGAACGTGCTACACGACCAGTGTACTATGGATTGTGGACATTT  
CCTTCTGTGGAGACACGGTGGAGAACTTAAACAATTTTTTAAAGCCACTATGGATTTAGTCAT  
CTGAATATGCTGTGCAGAAAAAATATGGGCTCCAGTGGTTTTTACCATGTCATTCTGAAATT  
TTTCTCTACTAGTTATGTTTGATTTCTTTAAGTTTCAATAAAATCATTTAGCATTGAAAAAAA

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**FIGURE 139**

MKFTIVFAGLLGVFLAPALANYNINVNDDNNNAGSGQQSVSVNNEHNVANVDNNNGWDSWNS  
IWDYGNGFAATRLFQKKTCIVHKMNKEVMPSIQSLDALVKEKKLQGKGPGGPPPKGLMYSVN  
PNKVDDLKFGKNIANMCRGIPTYMAEEMQEASLFFYSGTCYTTSVLWIVDISFCGDTVEN

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**FIGURE 140**

CATTTCTGAACTAATCGTGTCAGAATTGACTTTGAAAAGCATTGCTTTTTTACAGAAGTATA  
TTAACTTTTTAGGAGTAATTTCTAGTTTGGATTGTAATATGAAATAATTTAAAAGGGCTTCG  
CTCATATATAGGAAAATCGCATATGGTCCTAGTATTAAATTCTTATTGCTTACTGATTTTTT  
TGAGTTAAGAGTTGTTATATGCTAGAATATGAGGATGTGAATATAAATAAGAGAAGAAAAA  
GAATAAAGTAGATTGAGTCTCCAATTTTATGTAAGCTTCAGAAGAAGCTGGTTTGTTTACATG  
CAAGCTTATAGTTGAAATATTTTTTCAGGAATTACATGAATGACAGTCTTCGAACCAATGTGT  
TTGTTTCGATTTCAACCAGAGACTATAGCATGTGCTTGCATCTACCTTGCAGCTAGAGCACTT  
CAGATTCCGTTGCCAACTCGTCCCCATTGGTTTCTTCTTTTTTGGTACTACAGAAGAGGAAAT  
CCAGGAAATCTGCATAGAAACACTTAGGCTTTATACCAGAAAAAAGCCAAACTATGAATTAC  
TGGAAAAAGAAGTAGAAAAAAGAAAAGTAGCCTTACAAGAAGCCAAATTAAAAGCAAAGGGA  
TTGAATCCGGATGGAAGTCCAGCCCTTTCAACCCTGGGTGGATTTTCTCCAGCCTCCAAGCC  
ATCATCACCAAGAGAAGTAAAAGCTGAAGAGAAATCACCAATCTCCATTAATGTGAAGACAG  
TCAAAAAAGAACCTGAGGATAGACAACAGGCTTCCAAAAGCCCTTACAATGGTGTAAGAAAA  
GACAGCAAGAGAAGTAGAAATAGCAGAAGTGCAAGTCGATCGAGGTCAAGAACACGATCACG  
TTCTAGATCACATACTCCAAGAAGACACTATAATAATAGGCGGAGTCGATCTGGAACATACA  
GCTCGAGATCAAGAAGCAGGTCCCGCAGTCACAGTGAAAGCCCTCGAAGACATCATAATCAT  
GGTTCTCCTCACCTTAAGGCCAAGCATAACCAGAGATGATTTAAAAAGTTCAAACAGACATGG  
TCATAAAAGGAAAAAATCTCGTTCTCGATCTCAGAGCAAGTCTCGGGATCACTCAGATGCAG  
CCAAGAAACACAGGCATGAAAGGGGACATCATAGGGACAGGCGTGAACGATCTCGCTCCTTT  
GAGAGGTCCCATAAAAGCAAGCACCATGGTGGCAGTCGCTCAGGACATGGCAGGCACAGGCG  
CTGA

CTTTCTCTTCCTTTGAGCCTGCATCAGTTCTTGGTTTTGCCTATCTACAGTGTGATGT  
ATGGACTCAATCAAAAACATTAAACGCAAAGTATTAGGATTTGATTTCTTGAAACCCTCTA  
GGTCTCTAGAACACTGAGGACAGTTTCTTTTGAAAAGAACTATGTTAATTTTTTTTGCACATT  
AAAATGCCCTAGCAGTATCTAATTAAAAACCATGGTCAGGTTCAATTGTACTTTATTATAGT  
TGTGTATTGTTTATTGCTATAAGAACTGGAGCGTGAATTCTGTAAAAATGTATCTTATTTTT  
ATACAGATAAAATTGCAGACACTGTTCTATTTAAGTGGTTATTTGTTTAAATGATGGTGAAT  
ACTTTCTTAACACTGGTTTGTCTGCATGTGTAAAGATTTTTTACAAGGAAATAAAATACAAAT  
CTTGTTTTTTCTAAAAAAGT

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**FIGURE 141**

MNDSLRTNVFVRFPETIACACIYLAARALQIPLPTRPHWFLFLFGTTEEEIQEICIETLRLY  
TRKKPNYELLEKEVEK RKVALQEAKLKAKGLNPDGTPALSTLGGFSPASKPSSPREVKAEK  
SPISINVKTVKKEPEDRQQASKSPYNGVRKDSKRSRNSRSASRSRSRTRSRSRSHTPRRHYN  
NRRSRSGTYSSRSRSHSESPRRHHNHGSPHLKAKHTRDDLKSSNRHGHKRKKSRSRSQ  
SKSRDHSDAAKKHRHERGHHRDRRERSRSFERSHKSKHHGGSRSRSGHGRHR



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**FIGURE 142**

TGGGGATAAAGGAAAAATGGTCAGGTATTAATGGCTTAAAGATTATTGGAAGGGGTTTATCA  
TTTTTTGAANNNTATTCGGGTCANAATTGNCTTTGAAAAGCATTGCTTTTTTACAGAAATATAT  
TANCTTTTTAGAGTAATTTCTAGTTTGGATTGTAATATGAAATTATTTAAAAGGGCTTCGCT  
CATATATAGGAAAATCGCATATGGTCCTAGTATTAAATTNTTATTGCTTACTGATTTTTTTTG  
AGTTAAGAGTTGTTATATGNTAGAATATGAGGATGTGAATATAAATAAGAGAAGAAAAAAGA  
ATAAAGTAGATTGAGTCTCCAATTTTATGTAAGCTTCAGAAGAACTGGTTTGTTTACATGCA  
AGCTTATAGTTGAAATATTTTTTCAGGAATTACATGAATGACAGTCTTCGAACCAATGTGTTT  
GTTTCGATTTCAACCAGAGANTATAGCATGTGCTTGCATCTACCTTGCAGNTAGAGCACTTCA  
GATTCCGTTGCCAACTNGTCCCCATTGGTTTCTTCTTTTTTGGTACTACAGAAGAGGAAATCC  
AGGAAATNTGCATAGAAACACTTAGGCTTTATACCAGAAAAAAGCCAAACTATGAATTACTG  
GAAAAAGAAGTAGAAAAAAGAAAAGTAGCCTTACAAGAAGCCNAATTAAAAGCAAAGGGATT  
GAATCCGGATGGAACCTCCAGCCCTTTCAACCCTGGGTGGATTTTCTCC

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**FIGURE 143**

GGCACGAGGCCTCGTGCCAAGCTTGGCACGAGGGTGCACCGCGTTCTCGCACGCGTCAATGGC  
GGTCCTCGGAGTACAGCTGGTGGTGACCCTGCTCACTGCCACCCTCATGCACAGGCTGGCGC  
CACACTGCTCCTTCGCGCGCTGGCTGCTCTGTAAACGGCAGTTTGTTCGATAACAAGCACCCG  
TCTGAGGAGGAGCTTCGGGCCCCTGGCGGGGAAGCCGAGGCCAGAGGCAGGAAAGAGCGGTG  
GGCCAATGGCCTTAGTGAGGAGAAGCCACTGTCTGTGCCCCGAGATGCCCCGTTCCAGCTGG  
AGACCTGCCCCCTCACGACCGTGGATGCCCTGGTCTGCGCTTCTTCCTGGAGTACCAGTGG  
TTTGTGGACTTTGCTGTGTACTCGGGCGGCGTGTACCTCTTCACAGAGGCCTACTACTACAT  
GCTGGGACCAGCCAAGGAGACTAACATTGCTGTGTTCTGGTGCCTGCTCACGGTGACCTTCT  
CCATCAAGATGTTCTGACAGTGACACGGCTGTACTTCAGCGCCGAGGAGGGGGGTGAGCGC  
TCTGTCTGCCTCACCTTTGCCTTCCTCTTCCTGCTGCTGGCCATGCTGGTGCAAGTGGTGCG  
GGAGGAGACCCTCGAGCTGGGCCTGGAGCCTGGTCTGGCCAGCATGACCCAGAACTTAGAGC  
CACTTCTGAAGAAGCAGGGCTGGGACTGGGCGCTTCCTGTGGCCAAGCTGGCTATCCGCGTG  
GGACTGGCAGTGGTGGGCTCTGTGCTGGGTGCCTTCCTCACCTTCCCAGGCCTGCGGCTGGC  
CCAGACCCACCGGGACGCACTGACCATGTGCGAGGACAGACCCATGCTGCAGTTCCTCCTGC  
ACACCAGCTTCCTGTCTCCCCTGTTTCATCCTGTGGCTCTGGACAAAGCCCATTGCACGGGAC  
TTCCTGCACCAGCCGCGTTTGGGGAGACGCGTTTCTCCCTGCTGTCCGATTCTGCCTTCGA  
CTCTGGGCGCCTCTGGTTGCTGGTGGTGCTGTGCCTGCTGCGGCTGGCGGTGACCCGGCCCC  
ACCTGCAGGCCTACCTGTGCCTGGCCAAGGCCCGGGTGGAGCAGCTGCGAAGGGAGGCTGGC  
CGCATCGAAGCCCGTGAAATCCAGCAGAGGGTGGTCCGAGTCTACTGCTATGTGACCGTGGT  
GAGCTTGCAGTACCTGACGCCGCTCATCCTCACCTCAACTGCACACTTCTGCTCAAGACGC  
TGGGAGGCTATTCTGGGGCCTGGGCCCAGCTCCTCTACTATCCCCCGACCCATCCTCAGCC  
AGCGCTGCCCCCATCGGCTCTGGGGAGGACGAAGTCCAGCAGACTGCAGCGCGGATTGCCGG  
GGCCCTGGGTGGCCTGCTTACTCCCCTCTTCCTCCGTGGCGTCCTGGCCTACCTCATCTGGT  
GGACGGCTGCCTGCCAGCTGCTCGCCAGCCTTTTCGGCCTCTACTTCCACCAGCACTTGGCA  
GGCTCCTAGCTGCCTGCAGACCCTCCTGGGGCCCTGAGGTCTGTTCTGGGGCAGCGGGACA  
CTAGCCTGCCCCCTCTGTTTGCGCCCGGTGTCCCCAGCTGCAAGGTGGGGCCGGACTCCCC  
GGCGTTCCTTCACCACAGTGCTGACCCGCGGCCCCCTTGGACGCCGAGTTTCTGCCTCA  
GAACTGTCTCTCCTGGGCCCAGCAGCATGAGGGTCCCGAGGCCATTGTCTCCGAAGCGTATG  
TGCCAGGTTTGAGTGGCGAGGGTGATGCTGGCTGCTCTTCTGAACAAATAAAGGAGCATGCC  
GATTTTAA

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**FIGURE 144**

MAVLGVQLVVTLLTATLMHRLAPHCSFARWLLCNGSLFRYKHPSEEELRALAGKPRPRGRKE  
RWANGLSEEKPLSVPRDAPFQLETCPLTTVDALVLRFFLEYQWFVDFAVYSGGVYLFTEAYY  
YMLGPAKETNIAVFWCLLTVTFSIKMFLTVTRLYFSAEEGGERSVCLTFAFLFLLLAMLVQV  
VREETLELGLPGLASMTQNLEPLLKKQGWDWALPVAKLAIRVGLAVVGSVLGAFLTFFPGLR  
LAQTHRDALTMSEDRPMLQFLLHTSFLSPLFILWLWTKPIARDFLHQPPFGETRFSLLSDSA  
FDSGRLWLLVVLCLLRLAVTRPHLQAYLCLAKARVEQLRREAGRIEAREIQQRVVRVYCYVT  
VVSLQYLTPILITLNCTLLLKTLGGYSWGLGPAPLLSPDPSSASAAPIGSGEDEVQQTAARI  
AGALGGLLTPLFLRGVLAYLIWWTAACOLLASLFGLYFHQHLA

**FIGURE 145**

CGTTNGCACGCGTCAATGGCGGTCCTCGGAGTACAGCTGGTGGTGACCCTGCTCACTGCCAC  
CCTCATGCACAGGCTGGCGCCACACTGCTCCTTCGCGCGCTGGCTGCTCTGTAACGGCAGTT  
TGTTCCGATACAAGCACCCGTNTTGAGGAGGAGCTTCGGGGCCCTGGCGGGGAAGCCGAGGCC  
CAGAGGCAGGAAAGAGCGGTGGGCCAATGGCCTTAGTGAGGAGAAGCCACTGTCTGTGCCCC  
GAGATGCCCCGTTCCAGCTGGAGACCTGCCCCCTCACGACCGTGGATGCCCTGGTCCTGCGC  
TTCTTCCTGGAGTACCAGTGGTTTGTGGACTTTGCTGTGTACTCGGGCGGCGTGTACCTCTT  
CACAGAGGCCTACTACTACATGCTGGGACCAGCCAAGGAGACTAACATTGCTGTGTTCTGGT  
GCCTGCTCACAGTGACCTTCTCCATCAAGATGTTCCCTGACAGTGACACGGCTGTACTTCAGC  
GCCGAGGAGGGGGGTGAGCGCTCTGTCTGCCTCACCTTTGCCTTCCTCTTCCTGCTGCTGGC  
CATGCTGGTGCAAGCG



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## FIGURE 146

GGTTCCTACATCCTCTCATCTGAGAATCAGAGAGCATAATCTTCTTACGGGCCCCGTGATTTA  
TTAACGTGGCTTAATCTGAAGGTTCTCAGTCAAATTCTTTGTGATCTACTGATTGTGGGGGC  
ATGGCAAGGTTTGCTTAAAGGAGCTTGGCTGGTTTGGGCCCTTGTAGCTGACAGAAGGTGGC  
CAGGGAGAATGCAGCACACTGCTCGGAGAAATGAAGGCGCTTCTGTTGCTGGTCTTGCCTTGG  
CTCAGTCCTGCTAACTACATTGACAATGTGGGCAACCTGCACTTCCTGTATTCAGAACTCTG  
TAAAGGTGCCTCCCCTACGGCCTGACCAAAGATAGGAAGAGGCGCTCACAAGATGGCTGTC  
CAGACGGCTGTGCGAGCCTCACAGCCACGGCTCCCTCCCCAGAGGTTTCTGCAGCTGCCACC  
ATCTCCTTAATGACAGACGAGCCTGGCCTAGACAACCCTGCCTACGTGTCCTCGGCAGAGGA  
CGGGCAGCCAGCAATCAGCCCAGTGGACTCTGGCCGGAGCAACCGAACTAGGGCACGGCCCT  
TTGAGAGATCCACTATTAGAAGCAGATCATTTAAAAAATAAATCGAGCTTTGAGTGTTCTT  
CGAAGGACAAAGAGCGGGAGTGCAAGTTGCCAACCATGCCGACCAGGGCAGGGAAAATTCTGA  
AAACACCACTGCCCCCTGAAGTCTTTCCAAGGTTGTACCACCTGATTCCAGATGGTGAAATTA  
CCAGCATCAAGATCAATCGAGTAGATCCCAGTGAAAGCCTCTCTATTAGGCTGGTGGGAGGT  
AGCGAAACCCCACTGGTCCATATCATTATCCAACACATTTATCGTGATGGGGTGATCGCCAG  
AGACGGCCGGCTACTGCCAGGAGACATCATTCTAAAGGTCAACGGGATGGACATCAGCAATG  
TCCCTCACAACCTACGCTGTGCGTCTCCTGCGGCAGCCCTGCCAGGTGCTGTGGCTGACTGTG  
ATGCGTGAACAGAAGTTCCGCAGCAGGAACAATGGACAGGCCCCCGGATGCCTACAGACCCCG  
AGATGACAGCTTTCATGTGATTCTCAACAAAAGTAGCCCCGAGGAGCAGCTTGGAATAAAAC  
TGGTGCGCAAGGTGGATGAGCCTGGGGTTTTTCATCTTCAATGTGCTGGATGGCGGTGTGGCA  
TATCGACATGGTCAGCTTGAGGAGAATGACCGTGTGTTAGCCATCAATGGACATGATCTTCG  
ATATGGCAGCCCAGAAAGTGCGGCTCATCTGATTCAGGCCAGTGAAAGACGTGTTACCTCG  
TCGTGTCCCGCCAGGTTCCGGCAGCGGAGCCCTGACATCTTTCAGGAAGCCGGCTGGAACAGC  
AATGGCAGCTGGTCCCCAGGGCCAGGGGAGAGGAGCAACACTCCCAAGCCCCTCCATCCTAC  
AATTACTTGTATGAGAAGGTGGTAAATATCCAAAAAGACCCCGGTGAATCTCTCGGCATGA  
CCGTGCGCAGGGGGAGCATCACATAGAGAATGGGATTTGCCTATCTATGTCATCAGTGTTGAG  
CCCGGAGGAGTCATAAGCAGAGATGGAAGAATAAAAACAGGTGACATTTTGTGTAATGTGGA  
TGGGGTGAAGTCTGAGAGGTGAGCCGGAGTGAGGCAGTGGCATTATTGAAAAGAACATCAT  
CCTCGATAGTACTCAAAGCTTTGGAAGTCAAAGAGTATGAGCCCCAGGAAGACTGCAGCAGC  
CCAGCAGCCCTGGACTCCAACCACAACATGGCCCCACCCAGTGACTGGTCCCCATCCTGGGT  
CATGTGGCTGGAATTACCACGGTGCTTGTATAACTGTAAAGATATTGTATTACGAAGAAACA  
CAGCTGGAAGTCTGGGCTTCTGCATTGTAGGAGGTTATGAAGAATACAATGGAAACAAACCT  
TTTTTTCATCAAATCCATTGTTGAAGGAACACCAGCATACAATGATGGAAGAATTAGATGTGG  
TGATATTCTTCTTGCTGTCAATGGTAGAAGTACATCAGGAATGATACATGCTTGCTTGCGAA  
GACTGCTGAAAGAACTTAAAGGAAGAATTACTCTAACTATTGTTTCTTGGCCTGGCACTTTT  
TTATAGAAATCAATGATGGGTGAGAGGAAAACAGAAAAATCACAAATAGGCTAAGAAGTTGAA  
ACACTATATTTATCTTGTGAGTTTTTATATTTAAAGAAAGAATACATTGTAAAAATGTCAGG  
AAAAGTATGATCATCTAATGAAAGCCAGTTACACCTCAGAAAATATGATTCCAAAAAAATTA  
AACTACTAGTTTTTTTTTTCAGTGTGGAGGATTTCTCATTACTCTACAACATTGTTTATATTT  
TTTCTATTCAATAAAAAGCCCTAAAACAACATAAAATGATTGATTTGTATACCCCACTGAATT  
CAAGCTGATTTAAATTTAAATTTGGGTATATGCTGAAGTCTGCCAAGGGTACATTATGGCCA  
TTTTTAATTTACAGCTAAAATATTTTTTAAATGCATTGCTGAGAAACGTTGCTTTCATCAA  
ACAAGAATAAATATTTTTTCAGAAGTTAAA

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**FIGURE 147**

MKALLLLVLPWLSPANYIDNVGNLHFLYSELCKGASHYGLTKDRKRRSQDGCPCDGCASLTAT  
APSPEVSAAATISLMTDEPGLDNPAYVSSAEDGQPAISPVDSGRSNRTRARPFERSTIRSRS  
FKKINRALSVLRRTKSGSAVANHADQGRESENTTAPEVFPRLYHLIPDGEITSIKINRVDP  
SESLSIRLVGGSETPLVHII IQHIYRDGVIARDGRLLPGDII LKVNGMDISNVPHNYAVRLL  
RQPCQVLWLTVMREQKFRSRNNGQAPDAYRPRDDSFHVILNKSSPEEQLGIKLVRKVDEPGV  
FIFNVLDGGVAYRHGQLEENDRVLAINGHDLRYGSPESA AHLIQASERRVHLVVSQRQVRQRS  
PDIFQEAGWNSNGSWSPGPGERSNTPKPLHPTITCHEKVVNIQKDPGESLGMTVAGGASHRE  
WDLPIYVISVEPGGVISRDGRIKTGDILLNVDGVELTEVSRSEAVALLKRTSSSIVLKALEV  
KEYEPQEDCSSPAALDSNHNMAPPSDWSPSWVMWLELPRCLYNCKDIVLRRNTAGSLGFCIV  
GGYEEYNGNKPFPIKSIVEGTPAYNDGRIRCGDILLAVNGRSTSGMIHACLARLLKELKGRI  
TLTIVSWPGTFL

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**FIGURE 148**

CCAAAGTGATCATTTGAAAAAGAGATATCCACATCTTCAAGCCCATATAAAGGATAGAAGCT  
GCACAGGGCAGCTTTACTTACTCCAGCACCTTCCTCTCCCAGGCAAATGGTGCTGACCATCT  
TTGGGATACAATCTCATGGATACGAGGTTTTTAAACATCATCAGCCCAAGCAACAATGGTGGC  
AATG TTCAGGAGACAGTGACAATTGATAATGAAAAAATAACCGCCATCGTTAACATCCATGC  
AGGATCATGCTCTTCTACCACAATTTTTGACTATAAACATGGCTACATTGCATCCAGGGTGC  
TCTCCCGAAGAGCCTGCTTTATCCTGAAGATGGACCATCAGAACATCCCTCCTCTGAACAAT  
CTCCAATGGTACATCTATGAGAAACAGGCTCTGGACAACATGTTCTCCAACAAATACACCTG  
GGTCAAGTACAACCCTCTGGAGTCTCTGATCAAAGACGTGGATTGGTTCCTGCTTGGGTCAC  
CCATTGAGAACTCTGCAAACATATCCCTTTGTATAAGGGGGAAGTGGTTGAAAACACACAT  
AATGTCGGTGCTGGAGGCTGTGCAAAGGCTGGGCTCCTGGGCATCTTGGGAATTTCAATCTG  
TGCAGACATTCATGTTTTAGGATGATTAGCCCTCTTGTTTTATCTTTTCAAAGAAATACATCC  
TTGGTTTACACTCAAAGTCAAATTAAATTCTTTCCCAATGCCCCAACTAATTTTGAGATTC  
AGTCAGAAAATATAAATGCTGTATTTATA

**FIGURE 149**

MKILVAFLVLTIFGIQSHGYEVFNIISPSNNGGNVQETVTIDNEKNTAIVNIHAGSCSSTT  
IFDYKHGYIASRVLSRRACFILKMDHQNIPLNNLQWYIYEKQALDNMFSNKYTWVKYNPLE  
SLIKDVDWFLLGSPIEKLCKHIPLYKGEVVENTHNVGAGGCAKAGLLGILGISICADIHV



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**FIGURE 150**

GGCACGAGCCAGGAACTAGGAGGTTCTCACTGCCCCGAGCAGAGGCCCTACACCCACCGAGGC  
ATGGGGCTCCCTGGGCTGTTCTGCTTGGCCGTGCTGGCTGCCAGCAGCTTCTCCAAGGCACG  
GGAGGAAGAAATTACCCCTGTGGTCTCCATTGCCTACAAAGTCCTGGAAGTTTTCCCCAAAG  
GCCGCTGGGTGCTCATAACCTGCTGTGCACCCCAGCCACCACCGCCCATCACCTATTCCCTC  
TGTGGAACCAAGAACATCAAGGTGGCCAAGAAGGTGGTGAAGACCCACGAGCCGGCCTCCTT  
CAACCTCAACGTCACACTCAAGTCCAGTCCAGACCTGCTCACCTACTTCTGCCGGGCGTCCT  
CCACCTCAGGTGCCCATGTGGACAGTGCCAGGCTACAGATGCACTGGGAGCTGTGGTCCAAG  
CCAGTGTCTGAGCTGCGGGCCAACTTCACTCTGCAGGACAGAGGGGCAGGCCCCAGGGTGGA  
GATGATCTGCCAGGCGTCCTCGGGCAGCCACCTATCACCAACAGCCTGATCGGGAAGGATG  
GGCAGGTCCACCTGCAGCAGAGACCATGCCACAGGCAGCCTGCCAACTTCTCCTTCCTGCCG  
AGCCAGACATCGGACTGGTTCTGGTGCCAGGCTGCAAACAACGCCAATGTCCAGCACAGCGC  
CCTCACAGTGGTGCCCCCAGGTGGTGACCAGAAGATGGAGGACTGGCAGGGTCCCCTGGAGA  
GCCCCATCCTTGCCCTTGCCGCTCTACAGGAGCACCCGCCGTCTGAGTGAAGAGGAGTTTGGG  
GGGTTTCAGGATAGGGAATGGGGAGGTCAGAGGACGCAAAGCAGCAGCCATGTAGAATGAACC  
GTCCAGAGAGCCAAGCACGGCAGAGGACTGCAGGCCATCAGCGTGCACTGTTCGTATTTGGA  
GTTTCATGCAAAATGAGTGTGTTTTAGCTGCTCTTGCCACAAAAAAAAAAAAAAAAAAAAA.

**FIGURE 151**

MGLPGLFCLAVLAASSFSKAREEEITPVVSIAYKVLEVFPKGRWVLITCCAPQPPPPITYSL  
CGTKNIKVAKKVVKTHEPASFNLNVTCLKSSPDLLTYFCRASSTSGAHVDSARLQMHWELWSK  
PVSELNANFTLQDRGAGPRVEMICQASSGSPITNSLIGKDGQVHLQORPCHRQPANFSFLP  
SQTSDWFWCQAANNANVQHSALTVVPPGGDQKMEDWQGPLESPIALPLYRSTRRLSEEEFG  
GFRIGNGEVRGRKAAAM

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**FIGURE 152**

GGTCCTTAATGGCAGCAGCCGCCGCTACCAAGATCCTTCTGTGCCTCCCGCTTCTGCTCCTG  
CTGTCCGGCTGGTCCCGGGCTGGGCGAGCCGACCCTCACTCTCTTTGCTATGACATCACCGT  
CATCCCTAAGTTCAGACCTGGACCACGGTGGTGTGCGGTTCAAGGCCAGGTGGATGAAAAGA  
CTTTTCTTCACTATGACTGTGGCAACAAGACAGTCACACCTGTCAGTCCCCTGGGGAAGAAA  
CTAAATGTCACAACGGCCTGGAAAGCACAGAACCAGTACTGAGAGAGGTGGTGGACATACT  
TACAGAGCAACTGCGTGACATTCAGCTGGAGAATTACACACCCAAGGAACCCCTCACCCCTGC  
AGGCAAGGATGTCTTGTGAGCAGAAAGCTGAAGGACACAGCAGTGGATCTTGGCAGTTCAGT  
TTCGATGGGCAGATCTTCCTCCTCTTTGACTCAGAGAAGAGAATGTGGACAACGGTTCATCC  
TGGAGCCAGAAAGATGAAAGAAAAGTGGGAGAATGACAAGGTTGTGGCCATGTCCTTCCATT  
ACTTCTCAATGGGAGACTGTATAGGATGGCTTGAGGACTTCTTGATGGGCATGGACAGCACC  
CTGGAGCCAAGTGCAGGAGCACCACTCGCCATGTCCTCAGGCACAACCCAACCTCAGGGCCAC  
AGCCACCACCCTCATCCTTTGCTGCCTCCTCATCATCCTCCCCTGCTTCATCCTCCCTGGCA  
TCTGAGGAGAGTCCTTTAGAGTGACAGGTTAAAGCTGATACCAAAGGCTCCTGTGAGCACG  
GTCTTGATCAAACCTCGCCCTTCTGTCTGGCCAGCTGCCCACGACCTACGGTGTATGTCCAGT  
GGCCTCCAGCAGATCATGATGACATCATGGACCCAATAGCTCATTCACTGCCTTGATTCCTT  
TTGCCAACAATTTTACCAGCAGTTATACCTAACATATTATGCAATTTTCTCTTGGTGCTACC  
TGATGGAATTCCTGCACTTAAAGTTCTGGCTGACTAAACAAGATATATCATTTTCTTTCTTC  
TCTTTTTGTTTGGAAAATCAAGTACTTCTTTGAATGATGATCTCTTTCTTGCAAATGATATT  
GTCAGTAAAATAATCACGTTAGACTTCAGACCTCTGGGGATTCTTTCCGTGTCCTGAAAGAG  
AATTTTAAATTATTTAATAAGAAAAAATTTATATTAATGATTGTTTCCTTTAGTAATTTAT  
TGTTCTGTACTGATATTTAAATAAAGAGTTCTATTTCCCAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 153**

MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRWCAVQGQVDEKTFL  
HYDCGNKTVTPVSPLGKKLNVTAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLTLQAR  
MSCEQKAEGHSSGSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAMSFHYFS  
MGDCIGWLEDFLMGMDSTLEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPCFILPGI



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**FIGURE 154**

GGGAAAGCCATTTTCGAAAACCCATCTATACAACTATATATTTTCATTTCTGCTGCTAGCTG  
CCTTGGGCCTCACAATTTTCATTCTGTTTTCTGACTTTCAGTTATATACCGTGGAATGGAG  
TTGATCCCAACCATAACATCGTGGAGGGTTTTAATTTTGGTGGTAGCCCTCACCCAATTCTG  
GTGTGGCTTTCTTTGCAGAGGATTCCACCTTCAAATCATGAACTCTGGCTGTTGATCAAAA  
GAGAATTTGGATTCTACTCTAAAAGTCAATATAGGACTTGGCAAAAGAAGCTAGCAGAAGAC  
TCAACCTGGCCTCCCATAAACAGGACAGATTATTCAGGTGATGGCAAAAATGGATTCTACAT  
CAACGGAGGCTATGAAAGCCATGAACAGATTCCAAAAAGAAAACCTCAAATTGGGAGGCCAAC  
CCACAGAACAGCATTCTCTGGGCCAGGCTGTAATCAGAATTGTCGTCGTACATGCTCAACAGC  
ATTGCTTTTTTCCCCAAAATTAACACATTGTGGAGAAGTGATGATACTCTCCCCTTACCTTT  
CCTCTCTCCATTCAAGCATTCAAAGTATATTTTCAATGAATTAAACCTTGCAGCAAGGGACC  
TTAGATAGGCTTATTCTGACTGTATGCTTTACCAATGAGAGAAAAAAATGCATTTCTGTAT  
CATCCTTTTCAATAAACTGTATTCATTTTGAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 155**

MELIPTITSWRVLILVVALTQFWCGFLCRGFHLQNHFWLLIKREFGFYSKSQYRTWQKKLA  
EDSTWPPINRTDYSGDGKNGFYINGGYESHEQIPKRKLKLGGOPTQHFWARL

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**FIGURE 156**

GTTCTCCTTTCCGAGCCAAAATCCCAGGCGATGGTGAATTATGAACGTGCCACACCCATGAAG  
CTCTTGTGGCAGGTAACTGTGCACCACCACACCTGGAATGCCATCCTGCTCCCGTTCTGCTA  
CCTCACGGCGCAAGTGTGGATTCTGTGTGCAGCCATCGCTGCTGCCGCCCTCAGCCGGGCCCC  
AGAACTGCCCCCTCCGTTTGCTCGTGCAGTAACCAGTTCAGCAAGGTGGTGTGCACGCGCCGG  
GGCCTCTCCGAGGTCCCGCAGGGTATTCCCTCGAACACCCGGTACCTCAACCTCATGGAGAA  
CAACATCCAGATGATCCAGGCCGACACCTTCCGCCACCTCCACCACCTGGAGGTCTGCAGT  
TGGGCAGGAACTCCATCCGGCAGATTGAGGTGGGGGCCTTCAACGGCCTGGCCAGCCTCAAC  
ACCCTGGAGCTGTTGACAACCTGGCTGACAGTCATCCCTAGCGGGGCCTTTGAATACCTGTC  
CAAGCTGCGGGAGCTCTGGCTTCGCAACAACCCCATCGAAAGCATCCCCCTTTACGCCTTCA  
ACCGGGTGCCCTCCCTCATGCGCCTGGACTTGGGGGAGCTCAAGAAGCTGGAGTATATCTCT  
GAGGGAGCTTTTGAGGGGCTGTTCAACCTCAAGTATCTGAACTTGGGCATGTGCAACATTAA  
AGACATGCCCAATCTCACCCCCCTGGTGGGGCTGGAGGAGCTGGAGATGTCAGGGAACCACT  
TCCCTGAGATCAGGCCTGGCTCCTTCCATGGCCTGAGCTCCCTCAAGAAGCTCTGGGTCTATG  
AACTCACAGGTCAGCCTGATTGAGCGGAATGCTTTTGACGGGCTGGCTTCACTTGTGGAAC  
CAACTTGGCCCACAATAACCTCTCTTCTTTGCCCCATGACCTCTTTACCCCGCTGAGGTACC  
TGGTGGAGTTGCATCTACACCACAACCCTTGGAACCTGTGATTGTGACATTCTGTGGCTAGCC  
TGGTGGCTTCGAGAGTATATAACCCACCAATTCCACCTGCTGTGGCCGCTGTCATGCTCCCAT  
GCACATGCGAGGCCGCTACCTCGTGGAGGTGGACCAGGCCTCCTTCCAGTGCTCTGCCCCCT  
TCATCATGGACGCACCTCGAGACCTCAACATTTCTGAGGGTTCGGATGGCAGAACTTAAGTGT  
CGGACTCCCCCTATGTCCTCCGTGAAGTGGTTGCTGCCCAATGGGACAGTGCTCAGCCACGC  
CTCCCGCCACCCAAGGATCTCTGTCTCAACGACGGCACCTTGAACCTTTTCCCACGTGCTGC  
TTTCAGACACTGGGGTGTACACATGCATGGTGACCAATGTTGCAGGCAACTCCAACGCCTCG  
GCCTACCTCAATGTGAGCACGGCTGAGCTTAACACCTCCAACCTACAGCTTCTTCACCACAGT  
AACAGTGGAGACCACGGAGATCTCGCCTGAGGACACAACGCGAAAGTACAAGCCTGTTCTTA  
CCACGTCCACTGGTTACCAGCCGGCATATAACCACTCTACCACGGTGCTCATTACAGACTACC  
CGTGTGCCCAAGCAGGTGGCAGTACCCGCGACAGACACCACTGACAAGATGCAGACCAGCCT  
GGATGAAGTCATGAAGACCACCAAGATCATCATTGGCTGCTTTGTGGCAGTGACTCTGCTAG  
CTGCCGCCATGTTGATTGTCTTCTATAAACTTCGTAAGCGGCACCAGCAGCGGAGTACAGTC  
ACAGCCGCCCGGACTGTTGAGATAATCCAGGTGGACGAAGACATCCCAGCAGCAACATCCGC  
AGCAGCAACAGCAGCTCCGTCCGGTGTATCAGGTGAGGGGGCAGTAGTGCTGCCCACAATTC  
ATGACCATATTAATAACAACCTACAAACCAGCACATGGGGCCCACTGGACAGAAAACAGC  
CTGGGGAACTCTCTGCACCCACAGTCACCACTATCTCTGAACCTTATATAATTACAGCCCA  
TACCAAGGACAAGGTACAGGAACTCAAATATGACTCCCCCTCCCCCAAAAACTTATAAAAT  
GCAATAGAATGCACACAAAGACAGCAACTTTTGTACAGAGTGGGGAGAGACTTTTTCTTGTA  
TATGCTTATATATTAAGTCTATGGGCTGGTTAAAAAAACAGATTATATTAAATTTAAAGA  
CAAAAAGTCAAAACA

**FIGURE 157**

MKLLWQVTVHHHTWNAILLPFVYLTAQVWILCAAIAAAASAGPQNCPSVCSCSNQFSKVVCT  
RRGLSEVPQGIPSNTRYLNLMENNIQMIQADTFRHLHHLEVLQLGRNSIRQIEVGAFNGLAS  
LNTLELFDNWLTVIPSGAFEYLSKLRELWLRNNPIESIPSYAFNRVPSLMRLDLGELKKLEY  
ISEGAFEGLFNLKYLNLMCNKDMPNLTPLVGLEEELEMSGNHFPEIRPGSFHGLSSLKKLW  
VMNSQVSLIERNAFDGLASLVELNLAHNNLSSLPHDLFTPLRYLVELHLHHNPWNCDIILW  
LAWWLREYIPTNSTCCGRCHAPMHMRGRYLVEVDQASFQCSAPFIMDAPRDLNISEGRMAEL  
KCRTPPMSSVKWLLPNGTVLSHASRHPRISVLNDGTLNFSHVLLSDTGVYTCMVTNVAGNSN  
ASAYLNVSTAELNTSNYSFFTTVTVETTEISPEDTTRKYKPVPTTSTGYQPAYTTSTTVLIQ  
TTRVPKQVAVPATDITDKMQTSLDEVMKTTKIIIGCFVAVTLLAAAMLIVFYKLRKRHQORS  
TVTAARTVEIIQVDEDIPAATSAAATAAPSGVSGEGAVVLPTIHDHINYNTYKPAHGAHWTE  
NSLGNSLHPTVTTISEPYIIQTHTKDKVQETQI





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**FIGURE 159**

MELGCWTQLGLTFLQLLLISSLPREYTVINEACPGAENIMCRECCEYDQIECVCPGKREVV  
GYTIPCCRNEENECDSCLIHPGCTIFENCKSCRNGSWGGLDDFYVKGIFYCAECRAGWYGGD  
CMRCGQVLRAPKGQILLESYPLNAHCEWTIHAKPGFVIQLRFVMLSLEFDYMCQYDYVEVRD  
GDNRDGQIIKRVCGNERPAPIQSIGSSLHVLHFHSDGSKNFDGFFHAIYEEITACSSSPCFHDG  
TCVLDKAGSYKCACLAGYTGORCENLLEERNCSDPGGPVNGYQKITGGPGLINGRHAKIGTV  
VSFFCNNSYVLSGNEKRTCQONGEWSGKQPICIKACREPKISDLVRRRVLPQVQSRETPLH  
QLYSAAFSKQKLQSAPTKKPALPFGDLPMGYQHLHTQLQYECISPFYRRLGSSRRTCLRTGK  
WSGRAPSCIPICGKIENITAPKTQGLRWPWQAAIYRRTSGVHDGSLHKGAWFLVCSGALVNE  
RTVVVAHCVTDLGKVTMIKTADLKVVVLGKFYRDDDRDEKTIQSLQISAIILHPNYDPILLD  
ADIAILKLLDKARISTRVQPICLAASRDLSTSFOESHITVAGWNVLADVRSFGFKNDTLRSG  
VVSVDSSLCEEQHEDHGIPVSVTDNMFCASWEPTAPSDICTAETGGIAAVSFPGRASPEPR  
WHLMGLVSWSYDKTCSHRLSTAFTKVLPFKDWIERNMK

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**FIGURE 160**

ACCAGGCATTGTATCTTCAGTTGTCATCAAGTTCGCAATCAGATTGGAAAAGCTCAACTTGA  
AGCTTTCTTGCCCTGCAGTGAAGCAGAGAGATAGATATTATTCACGTAATAAAAAACATGGGC  
TTCAACCTGACTTTCCACCTTTCCTACAAATTCCGATTACTGTTGCTGTTGACTTTGTGCCT  
GACAGTGGTTGGGTGGGCCACCAGTAACTACTTCGTGGGTGCCATTCAAGAGATTCCTAAAG  
CAAAGGAGTTCATGGCTAATTTCCATAAGACCCTCATTTTGGGGAAGGGAAAACTCTGACT  
AATGAAGCATCCACGAAGAAGGTAGAACTTGACAACTGTCCTTCTGTGTCTCCTTACCTCAG  
AGGCCAGAGCAAGCTCATTTTCAAACCAGATCTCACTTTGGAAGAGGTACAGGCAGAAAATC  
CCAAAGTGTCAGAGGCCGGTATCGCCCTCAGGAATGTAAAGCTTTACAGAGGGTCGCCATCCTC  
GTTCCCCACCGGAACAGAGAGAAACACCTGATGTACCTGCTGGAACATCTGCATCCCTTCCT  
GCAGAGGCAGCAGCTGGATTATGGCATCTACGTCATCCACCAGGCTGAAGGTAAAAAGTTTA  
ATCGAGCCAACTCTTGAATGTGGGCTATCTAGAAGCCCTCAAGGAAGAAAATTGGGACTGC  
TTTATATTCCACGATGTGGACCTGGTACCCGAGAATGACTTTAACCTTTACAAGTGTGAGGA  
GCATCCCAAGCATCTGGTGGTTGGCAGGAACAGCACTGGGTACAGGTTACGTTACAGTGGAT  
ATTTTGGGGGTGTTACTGCCCTAAGCAGAGAGCAGTTTTTCAAGGTGAATGGATTCTCTAAC  
AACTACTGGGGATGGGGAGGCGAAGACGATGACCTCAGACTCAGGGTTGAGCTCCAAAGAAT  
GAAAATTTCCCGGCCCTGCCTGAAGTGGGTAAATATACAATGGTCTTCCACACTAGAGACA  
AAGGCAATGAGGTGAACGCAGAACGGATGAAGCTCTTACACCAAGTGTACAGAGTCTGGAGA  
ACAGATGGGTTGAGTAGTTGTTCTTATAAATTAGTATCTGTGGAACACAATCCTTTATATAT  
CAACATCACAGTGGATTTCTGGTTTGGTGCATGACCCTGGATCTTTTGGTGATGTTTGGAAAG  
AACTGATTCTTTGTTTGCAATAATTTTGGCCTAGAGACTTCAAATAGTAGCACACATTAAGA  
ACCTGTTACAGCTCATTGTTGAGCTGAATTTTTCTTTTTGTATTTTCTTAGCAGAGCTCCT  
GGTGATGTAGAGTATAAAACAGTTGTAACAAGACAGCTTCTTAGTCATTTTGATCATGAGG  
GTTAAATATTGTAATATGGATACTTGAAGGACTTTATATAAAAGGATGACTCAAAGGATAAA  
ATGAACGCTATTTGAGGACTCTGGTTGAAGGAGATTTATTTAAATTTGAAGTAATATATTAT  
GGGATAAAAGGCCACAGGAAATAAGACTGCTGAATGTCTGAGAGAACCAGAGTTGTTCTCGT  
CCAAGGTAGAAAGGTACGAAGATACAATACTGTTATTCAATTTATCCTGTACAATCATCTGTG  
AAGTGGTGGTGTGAGGTGAGAAGGCGTCCACAAAAGAGGGGAGAAAAGGCGACGAATCAGGA  
CACAGTGAACCTGGGAATGAAGAGGTAGCAGGAGGGTGGAGTGTGGCTGCAAAGGCAGCAG  
TAGCTGAGCTGGTTGCAGGTGCTGATAGCCTTCAGGGGAGGACCTGCCCAGGTATGCCTTCC  
AGTGATGCCCACCAGAGAATACATTCTCTATTAGTTTTTAAAGAGTTTTTGTAAAATGATTT  
TGTACAAGTAGGATATGAATTAGCAGTTTACAAGTTTACATATTAATAATAATAATATGT  
CTATCAAATACCTCTGTAGTAAAATGTGAAAAAGCAAAA

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**FIGURE 161**

MGFNLT FHLSYKFRLLLLLTLCLTVVGWATSNYFVGAIQEIPKAKEFMANFHKTLILGKGKT  
LTNEASTKKVELDNCPSVSPYLRGQSKLIFKPDLTLEEVQAENPKVSRGRYRPQECKALQRV  
AILVPHRNREKHLMYLLEHLHPFLQRQQLDYGIYVIHQAEKKFNRAKLLNVGYLEALKEEN  
WDCFIFHDVDLVPENDFNLYKCEEHPKHLVVGRNSTGYRLRYSGYFGGVTALSREQFFKVNG  
FSNNYWGWGGEDDDLRLRVELQRMKISRPLPEVGKYTMVFHTRDKGNEVNAERMKLLHQVSR  
VVRTDGLSSCSYKLVSVEHNPLYINITVDFWFGA

**Important features:**

**Signal peptide:**

amino acids 1-27

**N-glycosylation sites:**

amino acids 4-7, 220-223 and 335-338

**Xylose isomerase proteins:**

amino acids 191-201



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**FIGURE 162**

CGTGGGCCGGGGTTCGCGCAGCGGGCTGTGGGCGCGCCCCGGAGGAGCGACCGCCGCAGTTCTC  
GAGCTCCAGCTGCATTCCCTCCGCGTCCGCCCCACGCTTCTCCCGCTCCGGGGCCCCGCAATG  
GCCCAGGCAGTGTGGTCGCGCCTCGGCGCGCATCCTCTGGCTTGCTGCTCCTGCCCTGGGC  
CCCGGCAGGGGTGGCCGCAGGCCTGTATGAACTCAATCTCACCACCGATAGCCCTGCCACCA  
CGGGAGCGGTGGTGACCATCTCGGCCAGCCTGGTGGCCAAGGACAACGGCAGCCTGGCCCTG  
CCCGCTGACGCCCACCTCTACCGCTTCCACTGGATCCACACCCCCGCTGGTGCTTACTGGCAA  
GATGGAGAAGGGTCTCAGCTCCACCATCCGTGTGGTCCGCCACGTGCCCCGGGGAATTCCCGG  
TCTCTGTCTGGGTCACTGCCGCTGACTGCTGGATGTGCCAGCCTGTGGCCAGGGGGCTTTGTG  
GTCCTCCCCATCACAGAGTTCTCTGTGGGGGACCTTGTTGTCACCCAGAACACTTCCCTACC  
CTGGCCCAGCTCCTATCTCACTAAGACCGTCCCTGAAAGTCTCCTTCCTCCTCCACGACCCGA  
GCAACTTCCTCAAGACCGCCTTGTTTCTCTACAGCTGGGACTTCGGGGACGGGACCCAGATG  
GTGACTGAAGACTCCGTGGTCTATTATAACTATTCCATCATCGGGACCTTCACCGTGAAGCT  
CAAAGTGGTGGCGGAGTGGGAAGAGGTGGAGCCGGATGCCACGAGGGCTGTGAAGCAGAAGA  
CCGGGGACTTCTCCGCCTCGCTGAAGCTGCAGGAAACCCTTCGAGGCATCCAAGTGTTGGGG  
CCCACCCTAATTCAGACCTTCCAAAAGATGACCGTGACCTTGAACCTCCTGGGGAGCCCTCC  
TCTGACTGTGTGCTGGCGTCTCAAGCCTGAGTGCCTCCCGCTGGAGGAAGGGGAGTGCCACC  
CTGTGTCCGTGGCCAGCACAGCGTACAACCTGACCCACACCTTCAGGGACCCTGGGGACTAC  
TGCTTCAGCATCCGGGGCCGAGAATATCATCAGCAAGACACATCAGTACCACAAGATCCAGGT  
GTGGCCCTCCAGAATCCAGCCGGCTGTCTTTGCTTTCCCATGTGCTACACTTATCACTGTGA  
TGTTGGCCTTCATCATGTACATGACCCTGCGGAATGCCACTCAGCAAAAGGACATGGTGGAG  
AACCCGGAGCCACCCTCTGGGGTCAAGTGCTGCTGCCAGATGTGCTGTGGGCCTTTCTTGCT  
GGAGACTCCATCTGAGTACCTGGAAATTGTTCTGTGAGAACCACGGGCTGCTCCCGCCCCCTCT  
ATAAGTCTGTCAAACTTACACCGTGAGGCACTCCCCCTCCCCACCCCATCTCAGTGTTAA  
CTGACTGCTGACTTGAGTTTCCAGCAGGGTGGTGTGCACCACTGACCAGGAGGGGTTTATT  
TGCGTGGGGCTGTTGGCCTGGATCATCCATCCATCTGTACAGTTCAGCCACTGCCACAAGCC  
CCTCCCTCTCTGTCACCCCTGACCCAGCCATTACCCCATCTGTACAGTCCAGCCACTGACA  
TAAGCCCCACTCGGTTACCACCCCCTTGACCCCTACCTTTGAAGAGGCTTCGTGCAGGACT  
TTGATGCTTGGGGTGTTCGGTGTGACTCCTAGGTGGGCCTGGCTGCCCACTGCCCATTCCT  
CTCATATTGGCACATCTGCTGTCCATTGGGGGTTCTCAGTTTCCTCCCCCAGACAGCCCTAC  
CTGTGCCAGAGAGCTAGAAAGAAGGTCAATAAGGGTTAAAAATCCATAACTAAAGGTTGTAC  
ACATAGATGGGCACACTCACAGAGAGAAGTGTGCATGTACACACACCACACACACACACACA  
CACACACACACAGAAATATAAACACATGCGTCACATGGGCATTTTCAGATGATCAGCTCTGTA  
TCTGGTTAAGTCGGTTGCTGGGATGCACCCTGCACTAGAGCTGAAAGGAAATTTGACCTCCA  
AGCAGCCCTGACAGGTTCTGGGCCCCGGGCCCTCCCTTTGTGCTTTGTCTCTGCAGTTCTTGC  
GCCCTTTATAAGGCCATCCTAGTCCCTGCTGGCTGGCAGGGGCCTGGATGGGGGGCAGGACT  
AATACTGAGTGATTGCAGAGTGCTTTATAAATATCACCTTATTTTATCGAAACCCATCTGTG  
AACTTTCACTGAGGAAAAGGCCTTGACGCGGTAGAAGAGGTTGAGTCAAGGCCGGGCGCGG  
TGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGTGGATCACGAGATCAGGA  
GATCGAGACCACCCTGGCTAACACGGTGAAACCCCGTCTCTACTAAAAAATACAAAAAGTT  
AGCCGGGCGTGGTGGTGGGTGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATG  
GTGCGAACCCGGGAGGCGGAGCTTGCAGTGAGCCCAGATGGCGCCACTGCACTCCAGCCTGA  
GTGACAGAGCGAGACTCTGTCTCCA

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**FIGURE 163**

MAQAVWSRLGRILWLACLLPWAPAGVAAGLYELNLTTDSPATTGAVVTISASLVAKDNGSLA  
LPADAHLYRFHWIHTPLVLTGKMEKGLSSTIRVVGHVPGEFPVSVWVTAADCWMCQPVARGF  
VVLPI TEFLVGDLVVTQNTSLPWPS SYLT KT V L K V S F L L H D P S N F L K T A L F L Y S W D F G D G T Q  
MVTEDSVVYYNYSIIGTFTVKLKVVAEWEEVEPDATRAVKQKTGDFSASLKLQETLRGIQVL  
GPTLIQTFQKMTVTNLNFLGSPPLTVCWRLKPECLPLEEGECHPVSVASTAYNLTHTRDPGD  
YCFSIRAENIISKTHQYHKIQVWPSRIQPAVFAFPCATLITVMLAFIMYMTLRNATQQKDMV  
ENPEPPSGVRCCCQMC CGPFLLET PSEYLEIVRENHGLLPPLYKSVKTYTV

**Important features of the protein:**

**Signal peptide:**

amino acids 1-24

**Transmembrane domain:**

amino acids 339-362

**N-glycosylation sites.**

amino acids 34-37, 58-61, 142-145, 197-200, 300-303 and 364-367



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**FIGURE 165**

MALSSQIWAACLLLLLLLLASLTSGSVFPQQTGQLAELQPQDRAGARASWMPMFQRRRRRDTH  
FPICIFCCGCCHRSKCGMCCKT



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**FIGURE 166**

CTGTCAGGAAGGACCATCTGAAGGCTGCAATTTGTTCTTAGGGAGGCAGGTGCTGGCCTGGC  
CTGGATCTTCCACCATGTTCTGTTGCTGCCTTTTGATAGCCTGATTGTCAACCTTCTGGGC  
ATCTCCCTGACTGTCCTCTTCACCCTCCTTCTCGTTTTTCATCATAGTGCCAGCCATTTTTTGG  
AGTCTCCTTTGGTATCCGCAAACCTCTACATGAAAAGTCTGTTAAAAATCTTTGCGTGGGCTA  
CCTTGAGAATGGAGCGAGGAGCCAAGGAGAAGAACCACCAGCTTTACAAGCCCTACACCAAC  
GGAATCATTGCAAAGGATCCCACCTTCACTAGAAGAAGAGATCAAAGAGATTCTGTCGAAGTGG  
TAGTAGTAAGGCTCTGGACAACACTCCAGAGTTCGAGCTCTCTGACATTTTCTACTTTTGCC  
GGAAAGGAATGGAGACCATTTATGGATGATGAGGTGACAAAGAGATTCTCAGCAGAAGAACTG  
GAGTCCTGGAACCTGCTGAGCAGAACCAATTATAACTTCCAGTACATCAGCCTTCGGCTCAC  
GGTCCTGTGGGGGTTAGGAGTGCTGATTCGGTACTGCTTTCTGCTGCCGCTCAGGATAGCAC  
TGGCTTTTACAGGGATTAGCCTTCTGGTGGTGGGCACAACCTGTGGTGGGATACTTGCCAAAT  
GGGAGGTTTAAGGAATTCATGAGTAAACATGTTCACTTAATGTGTTACCGGATCTGCGTGCG  
AGCGCTGACAGCCATCATCACCTACCATGACAGGGAAAACAGACCAAGAAATGGTGGCATCT  
GTGTGGCCAATCATACTCACCGATCGATGTGATCATCTTGGCCAGCGATGGCTATTATGCC  
ATGGTGGGTCAAGTGCACGGGGGACTCATGGGTGTGATTCAGAGAGCCATGGTGAAGGCCTG  
CCCACACGTCTGGTTTGAGCGCTCGGAAGTGAAGGATCGCCACCTGGTGGCTAAGAGACTGA  
CTGAACATGTGCAAGATAAAAGCAAGCTGCCTATCCTCATCTTCCCAGAAGGAACCTGCATC  
AATAATACATCGGTGATGATGTTCAAAAAGGGGAAGTTTTGAAATTGGAGCCACAGTTTACCC  
TGTTGCTATCAAGTATGACCCTCAATTTGGCGATGCCTTCTGGAACAGCAGCAAATACGGGA  
TGGTGACGTACCTGCTGCGAATGATGACCAGCTGGGCCATTGTCTGCAGCGTGTGGTACCTG  
CCTCCCATGACTAGAGAGGCAGATGAAGATGCTGTCCAGTTTGCGAATAGGGTGAAATCTGC  
CATTGCCAGGCAGGGAGGACTTGTGGACCTGCTGTGGGATGGGGGCCTGAAGAGGGAGAAGG  
TGAAGGACACGTTCAAGGAGGAGCAGCAGAAGCTGTACAGCAAGATGATCGTGGGGAACCAC  
AAGGACAGGAGCCGCTCCTTGAGGCCTGCCTCCAGCTGGCTGGGGCCACCGTGCGGGGTGCCAA  
CGGGCTCAGAGCTGGAGTTGCCGCCGCCGCCCCCACTGCTGTGTCTTTCCAGACTCCAGGG  
CTCCCCGGGCTGCTCTGGATCCCAGGACTCCGGCTTTCGCCGAGCCGCAGCGGGATCCCTGT  
GCACCCGGCGCAGCCTACCCTTGGTGGTCTAAACGGATGCTGCTGGGTGTTGCGACCCAGGA  
CGAGATGCCTTGTTTTCTTTTACAATAAGTCGTTGGAGGAATGCCATTAAAGTGAACCTCCCCA  
CCTTTGCACGCTGTGCGGGCTGAGTGGTTGGGGAGATGTGGCCATGGTCTTGTGCTAGAGAT  
GGCGGTACAAGAGTCTGTTATGCAAGCCCGTGTGCCAGGGATGTGCTGGGGGCGGCCACCCG  
CTCTCCAGGAAAGGCACAGCTGAGGCACTGTGGCTGGCTTCGGCCTCAACATCGCCCCCAGC  
CTTGAGCTCTGCAGACATGATAGGAAGGAAACTGTCATCTGCAGGGGCTTTCAGCAAATG  
AAGGGTTAGATTTTTATGCTGCTGCTGATGGGGTTACTAAAGGGAGGGGAAGAGGCCAGGTG  
GGCCGCTGACTGGGCCATGGGGAGAACGTGTGTTCTGTAATCCAGGCTAACCTGAACTCCCC  
ATGTGATGCGCGCTTTGTTGAATGTGTGTCTCGGTTTCCCCATCTGTAATATGAGTCGGGGG  
GAATGGTGGTGATTCCTACCTCACAGGGCTGTTGTGGGGATTAAAGTGCTGCGGGTGAGTGA  
AGGACACATCAGTTCAAGTGTTCAGGTACAGGCCACAAAACGGGGCACGGCAGGCCTGAG  
CTCAGAGCTGCTGCACTGGGCTTTGGATTTGTTCTTGTGAGTAAATAAAACTGGCTGGTGAATGA

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**FIGURE 167**

MFLLLPFDSLIVNLLGISLTVLFTLLLVFIIVPAIFGVSFQIRKLYMKSLLKIFAWATLRME  
RGAKEKNHQLYKPYTNGIIAKDPTSLEEEIKEIRRSKSSKALDNTPEFELSDIFYFCRKGME  
TIMDDEVTKRFSAEELSWNLLSRTNYNFQYISLRLTVLWGLGVLIRYCFLPLRIALAFTG  
ISLLVVGTTVVGYPNGRFKEFMSKHVHLMCYRICVRALTAIITYHDRENRPNGGICVANH  
TSPIDVILASDGYAMVGQVHGGLMGVIQRAMVKACPHVWFERSEVKDRHLVAKRLTEHVQ  
DKSKLPILIFPEGTCINNTSVMMFKKGSFEIGATVYPVAIKYDPQFGDAFWNSSKYGMVTYL  
LRMMTSWAIVCSVWYLPPMTREADEDAVQFANRVKSAIARQGGLVDLLWDGGLKREKVKDTF  
KEEQQKLYSKMIVGNHKDRSRS

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**FIGURE 168**

GCCCCTCGAAACCAGGACTCCAGCACCTCTGGTCCCGCCCTCACCCGGACCCCTGGCCCTCA  
CGTCTCCTCCAGGGATGGCGCTGGCGGCTTTGATGATCGCCCTCGGCAGCCTCGGCCTCCAC  
ACCTGGCAGGCCCAGGCTGTTCCCACCATCCTGCCCCCTGGGCCTGGCTCCAGACACCTTTGA  
CGATACCTATGTGGGTTGTGCAGAGGAGATGGAGGAGAAGGCAGCCCCCTGCTAAAGGAGG  
AAATGGCCCACCATGCCCTGCTGCGGGAATCCTGGGAGGCAGCCAGGAGACCTGGGAGGAC  
AAGCGTCGAGGGCTTACCTTGCCCCCTGGCTTCAAAGCCCAGAATGGAATAGCCATTATGGT  
CTACACCAACTCATCGAACACCTTGTACTGGGAGTTGAATCAGGCCGTGCGGACGGGCGGAG  
GCTCCCGGGAGCTCTACATGAGGCACTTTCCCTTCAAGGCCCTGCATTTCTACCTGATCCGG  
GCCCTGCAGCTGCTGCGAGGCAGTGGGGGCTGCAGCAGGGGACCTGGGGAGGTGGTGTTCG  
AGGTGTGGGCAGCCTTCGCTTTGAACCCAAGAGGCTGGGGGACTCTGTCCGCTTGGGCCAGT  
TTGCCTCCAGCTCCCTGGATAAGGCAGTGGCCACAGATTTGGGGAGAAGAGGCGGGGCTGT  
GTGTCTGCGCCAGGGGTGCAGCTAGGGTCACAATCTGAGGGGGCCTCCTCTCTGCCCCCTG  
GAAGACTCTGCTCTTGGCCCCCTGGAGAGTTCCAGCTCTCAGGGGTTGGGCCCTTGAAAGTCCA  
ACATCTGCCACTTAGGAGCCCTGGGAACGGGTGACCTTCATATGACGAAGAGGCACCTCCAG  
CAGCCTTGAGAAGCAAGAACATGGTTCCGGACCCAGCCCTAGCAGCCTTCTCCCCAACCAGG  
ATGTTGGCCTGGGGAGGCCACAGCAGGGCTGAGGGAACCTCTGCTATGTGATGGGGACTTCCT  
GGGACAAGCAAGGAAAGTACTGAGGCAGCCACTTGATTGAACGGTGTTGCAATGTGGAGACA  
TGGAGTTTTATTGAGGTAGCTACGTGATTAAATGGTATTGCAGTGTGGA

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**FIGURE 169**

MALAALMIALGSLGLHTWQAQAVPTILPLGLAPDTFDDTYVGCAEEMEEKAAPLLKEEMAHH  
ALLRESWEAAQETWEDKRRGLTLPPGFKAQNGIAIMVYTNSSNTLYWELNQAVRTGGGSREL  
YMRHFPFKALHFYLIRALQLLRGSGGCSRGPGEVVFRGVGSLRFEPKRLGDSVRLGQFASSS  
LDKAVAHRFGEKRRGCVSAPGVQLGSQSEGASSLPPWKTL L LAPGEFQLSGVGP



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**FIGURE 170**

GTGGCTTCATTTTCAGTGGCTGACTTCCAGAGAGCAATATGGCTGGTTCCTCCCAACATGCCTCA  
CCCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCCTCTGGACCCGTGAAAGAGCTG  
GTCGGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTCCAAAGTAAAGCAAGTTGACTC  
TATTGTCTGGACCTTCAACACAACCCCTCTTGTCACCATAACAGCCAGAAGGGGGCACTATCA  
TAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCAGATGGAGGCTACTCCCTGAAG  
CTCAGCAAACCTGAAGAAGAATGACTCAGGGATCTACTATGTGGGGATATACAGCTCATCACT  
CCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACGAGCACCTGTCAAAGCCTAAAG  
TCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTGACCAATCTGACATGCTGCATG  
GAACATGGGGAAGAGGATGTGATTTATACCTGGAAGGCCCTGGGGCAAGCAGCCAATGAGTC  
CCATAATGGGTCCATCCTCCCCATCTCCTGGAGATGGGGAGAAAGTGATATGACCTTCATCT  
GCGTTGCCAGGAACCCTGTCAGCAGAACTTCTCAAGCCCCATCCTTGCCAGGAAGCTCTGT  
GAAGGTGCTGCTGATGACCCAGATTCTCCATGGTCCTCCTGTGTCTCCTGTTGGTGCCCT  
CCTGCTCAGTCTCTTTGTACTGGGGCTATTTCTTTGGTTTCTGAAGAGAGAGAGACAAGAAG  
AGTACATTGAAGAGAAGAAGAGAGTGGACATTTGTCTGGGAAACTCCTAACATATGCCCCCAT  
TCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAATAGAACAATCCTAAAGGAAGA  
TCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAAAGATGGAAAATCCCCACTCAC  
TGCTCACGATGCCAGACACACCAAGGCTATTTGCCTATGAGAATGTTATCTAGACAGCAGTG  
CACTCCCCTAAGTCTCTGCTCA

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**FIGURE 171**

MAGSPTCLTLIYILWQLTGSAASGPVKELVGSVGGAVTFPLKSKVKQVDSIVWTFNTTPLVT  
IQPEGGTIIIVTQNRNRERVDFPDGGYSLKLSKLKKNDSGIYYVGIYSSSLQQPSTQEYVLHV  
YEHLSPKVTMGLQSNKNGTCVTNLTCMEHGEEDVIYTWKALGQAANESHNGSILPISWRW  
GESDMTFICVARNPVSRNFSSPILARKLCEGAADDPDSSMVLLCLLLVPLLLSLFVLGLFLW  
FLKRERQEEYIEEKKRVDICRETPNICPHSGENTHEYDTIPHTNRTILKEDPANTVYSTVEIP  
KKMENPHSLLTMPDTPRLFAYENVI

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**FIGURE 172**

CTGGTTCCCCAACATGCCTCACCTCATCTATATCCTTTGGCAGCTCACAGGGTCAGCAGCC  
TCTGGACCCCGTGAAAGAGCTGGTCCGTTCCGTTGGTGGGGCCGTGACTTTCCCCCTGAAGTC  
CAAAGTAAAGCAAGTTGACTCTATTGTCTGGACCTTCAACACAACCCCTCTTGTACCATAC  
AGCCAGAAGGGGGCACTATCATAGTGACCCAAAATCGTAATAGGGAGAGAGTAGACTTCCCA  
GATGGAGGCTACTCCCTGAAGCTCAGCAAACCTGAAGAAGAATGACTCAGGGATCTACTATGT  
GGGGATATACAGCTCATCACTCCAGCAGCCCTCCACCCAGGAGTACGTGCTGCATGTCTACG  
AGCACCTGTCAAAGCCTAAAGTCACCATGGGTCTGCAGAGCAATAAGAATGGCACCTGTGTG  
ACCAATCTGACATGCTGCATGGAACATGGGGAAGAGGATGTGATTTATACCTGGAAGGCCCT  
GGGGCAAGCAGCCAATGAGTCCCATAATGGGTCCATCCTCCCCATCTCCTGGAGATGGGGAG  
AAAGTGATATGACCTTCATCTGCGTTGCCAGGAACCCTGTCAGCAGAACTTCTCAAGCCCC  
ATCCTTGCCAGGAAGCTCTGTGAAGGTGCTGCTGATGACCCAGATTCTCCATGGTCCTCCT  
GTGTCTCCTGTTGGTGCCCCCTCCTGCTCAGTCTCTTTGTACTGGGGCTATTTCTTTGGTTTC  
TGAAGAGAGAGAGACAAGAAGAGTACATTGAAGAGAAGAAGAGAGTGGACATTTGTCGGGAA  
ACTCCTAACATATGCCCCCATCTCTGGAGAGAACACAGAGTACGACACAATCCCTCACACTAA  
TAGAACAATCCTAAAGGAAGATCCAGCAAATACGGTTTACTCCACTGTGGAAATACCGAAAA  
AGATGGAAAATCCCCACTCACTGCTCACGATGCCAGACACACCAAGGCTATTTGCCTATGAG  
AATGTTATCTAGACAGCAGTGCACTCCCCTAAGTCTCTGCTCAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 173**

GAAAGACGTGGTCCTGACAGACAGACAATCCTATTCCCTACCAAAATGAAGATGCTGCTGCT  
GCTGTGTTTGGGACTGACCCTAGTCTGTGTCCATGCAGAAGAAGCTAGTTCTACGGGAAGGA  
ACTTTAATGTAGAAAAGATTAATGGGGAATGGCATACTATTATCCTGGCCTCTGACAAAAGA  
GAAAAGATAGAAGAACATGGCAACTTTAGACTTTTTCTGGAGCAAATCCATGTCTTGAGAA  
TTCCTTAGTTCTTAAAGTCCATACTGTAAGAGATGAAGAGTGCTCCGAATTATCTATGGTTG  
CTGACAAAACAGAAAAGGCTGGTGAATATTCTGTGACGTATGATGGATTCAATACATTTACT  
ATACCTAAGACAGACTATGATAACTTTCTTATGGCTCACCTCATTAACGAAAAGGATGGGGA  
AACCTTCCAGCTGATGGGGCTCTATGGCCGAGAACCAGATTTGAGTTCAGACATCAAGGAAA  
GGTTTGCACAACCTATGTGAGGAGCATGGAATCCTTAGAGAAAATATCATTGACCTATCCAAT  
GCCAATCGCTGCCTCCAGGCCCGAGAATGAAGAATGGCCTGAGCCTCCAGTGTTGAGTGGAC  
ACTTCTCACCAGGACTCCACCATCATCCCTTCCTATCCATACAGCATCCCCAGTATAAATTC  
TGTGATCTGCATTCCATCCTGTCTCACTGAGAAGTCCAATTCCAGTCTATCAACATGTTACC  
TAGGATACCTCATCAAGAATCAAAGACTTCTTTAAATTTCTCTTTGATACACCCTTGACAAT  
TTTTCATGAAATTATTCCTCTTCCTGTTCAATAAATGATTACCCTTGCACTTAA



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**FIGURE 174**

MKMLLLLCLGLTLVCVHAEESSTGRNFNVEKINGEWHTIILASDKREKIEEHGNFRLFLEQ  
IHVLENSLV LKVHTVRDEECSELSMVADKTEKAGEYSVTYDGFNTFTIPKTDYDNFLMAHLI  
NEKDGETFQLMGLYGREPDLS DIKERFAQLCEEHGILRENIIDLSNANRCLQARE

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**FIGURE 175**

GGCTCGAGCGTTTCTGAGCCAGGGGTGACCATGACCTGCTGCGAAGGATGGACATCCTGCAA  
TGGATTCAGCCTGCTGGTTCTACTGCTGTTAGGAGTAGTTCTCAATGCGATACCTCTAATTG  
TCAGCTTAGTTGAGGAAGACCAATTTTCTCAAACCCCATCTCTTGCTTTGAGTGGTGGTTC  
CCAGGAATTATAGGAGCAGGTCTGATGGCCATTCCAGCAACAACAATGTCCTTGACAGCAAG  
AAAAAGAGCGTGCTGCAACAACAGAACTGGAATGTTTCTTTCATCATTTTTCAGTGTGATCA  
CAGTCATTGGTGCTCTGTATTGCATGCTGATATCCATCCAGGCTCTCTTAAAAGGTCCTCTC  
ATGTGTAATTCTCCAAGCAACAGTAATGCCAATTGTGAATTTTCATTGAAAAACATCAGTGA  
CATTCATCCAGAATCCTTCAACTTGCAGTGGTTTTTCAATGACTCTTGTGCACCTCCTACTG  
GTTTCAATAAACCCACCAGTAACGACACCATGGCGAGTGGCTGGAGAGCATCTAGTTTCCAC  
TTCGATTCTGAAGAAAACAAACATAGGCTTATCCACTTCTCAGTATTTTATAGGTCTATTGCT  
TGTTGGAATTCTGGAGGTCCTGTTTGGGCTCAGTCAGATAGTCATCGGTTTCCTTGGCTGTC  
TGTGTGGAGTCTCTAAGCGAAGAAGTCAAATTGTGTAGTTTAATGGGAATAAAATGTAAGTA  
TCAGTAGTTTGAAAAAAAAAAAA

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**FIGURE 176**

MTCCEGWTSCNGFSLLVLLLLGVVLNAIPLIVSLVEEDQFSQNPISCFEWWFPGIIGAGLMA  
IPATTMSLTARKRACCNNRTGMFLSSFFSVITVIGALYCMLISIQALLKGPLMCNSPSNSNA  
NCEFSLKNISDIHPESFNLQWFFNDSCAPPTGFNKPTSNDTMASGWRASSFHFDSEENKHRL  
IHFSVFLGLLLVGILEVLFGLSQIVIGFLGCLCGVSKRRSQIV

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**FIGURE 177**

GTCGAATCCAAATCACTCATTGTGAAAGCTGAGCTCACAGCCGAATAAGCCACCAATGAGGCT  
GTCAGTGTGTCTCCTGATGGTCTCGCTGGCCCTTTGCTGCTACCAGGCCCATGCTCTTGTCT  
GCCCAGCTGTTGCTTCTGAGATCACAGTCTTCTTATTCTTAAGTGACGCTGCGGTAAACCTC  
CAAGTTGCCAAACTTAATCCACCTCCAGAAGCTCTTGCAGCCAAGTTGGAAGTGAAGCACTG  
CACCGATCAGATATCTTTTAAGAAACGACTCTCATTGAAAAAGTCCTGGTGGAAATAGTGAA  
AAAATGTGGTGTGTGACATGTAAAAATGCTCAACCTGGTTTCCAAAGTCTTTCAACGACACC  
CTGATCTTCACTAAAAATTGTAAAGGTTTCAACACGTTGCTTTAATAAATCACTTGCCCTGC



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**FIGURE 178**

MRLSVCLLMVSLALCCYQAHALVCPAVASEITVFLFLSDAAVNQLQVAKLNPPPEALAAKLEV  
KHCTDQISFKKRLSLKKSWWK

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**FIGURE 179**

ATCCGTTCTCTGCGCTGCCAGCTCAGGTGAGCCCTCGCCAAGGTGACCTCGCAGGACACTGG  
TGAAGGAGCAGTGAGGAACCTGCAGAGTCACACAGTTGCTGACCAATTGAGCTGTGAGCCTG  
GAGCAGATCCGTGGGCTGCAGACCCCCGCCCCAGTGCCTCTCCCCCTGCAGCCCTGCCCCCTC  
GAACTGTGACATGGGAGAGAGTGACCCTGGCCCTTCTCCTACTGGCAGGCCTGACTGCCTTGG  
AAGCCAATGACCCATTTGCCAATAAAGACGATCCCTTCTACTATGACTGGAAAAACCTGCAG  
CTGAGCGGACTGATCTGCGGAGGGCTCCTGGCCATTGCTGGGATCGCGGCAGTTCTGAGTGG  
CAAATGCAAATACAAGAGCAGCCAGAAGCAGCACAGTCCTGTACCTGAGAAGGCCATCCCAC  
TCATCACTCCAGGCTCTGCCACTACTTGCTTGAGCACAGGACTGGCCTCCAGGGATGGCCTGA  
AGCCTAACACTGGCCCCCAGCACCTCCTCCCCTGGGAGGCCTTATCCTCAAGGAAGGACTTC  
TCTCCAAGGGCAGGCTGTTAGGCCCCTTTCTGATCAGGAGGCTTCTTTATGAATTAAACTCG  
CCCCACCACCCCCTCA

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**FIGURE 180**

MERVTLALLLLAGLTALEANDPFANKDDPFYYDWKNLQLSGLICGGLLAIAAGIAAVLSGKCK  
YKSSQKQHSPVPEKAIPITPGSATTC

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**FIGURE 181**

GGAGAAGAGGTTGTGTGGGACAAGCTGCTCCCGACAGAAGGATGTCGCTGCTGAGCCTGCCC  
TGGCTGGGCCTCAGACCGGTGGCAATGTCCCCATGGCTACTCCTGCTGCTGGTTGTGGGCTC  
CTGGCTACTCGCCCGCATCCTGGCTTGGACCTATGCCTTCTATAACAACTGCCGCCGGCTCC  
AGTGTTTCCCACAGCCCCCAAACGGAAGTGGTTTTGGGGTCACCTGGGCCTGATCACTCCT  
ACAGAGGAGGGCTTGAAGGACTCGACCCAGATGTCGGCCACCTATTCCCAGGGCTTTACGGT  
ATGGCTGGGTCCCATCATCCCCTTCATCGTTTTATGCCACCCTGACACCATCCGGTCTATCA  
CCAATGCCTCAGCTGCCATTGCACCCAAGGATAATCTCTTCATCAGGTTCTGAAGCCCTGG  
CTGGGAGAAGGGATACTGCTGAGTGGCGGTGACAAGTGGAGCCGCCACCGTCGGATGCTGAC  
GCCCCGCTTCCATTTCAACATCCTGAAGTCCTATATAACGATCTTCAACAAGAGTGCAAACA  
TCATGCTTGACAAGTGGCAGCACCTGGCCTCAGAGGGCAGCAGTCGTCTGGACATGTTTGAG  
CACATCAGCCTCATGACCTTGGACAGTCTACAGAAATGCATCTTCAGCTTTGACAGCCATTG  
TCAGGAGAGGCCAGTGAATATATTGCCACCATCTTGGAGCTCAGTGCCCTTGTAGAGAAAA  
GAAGCCAGCATATCCTCCAGCACATGGACTTTCTGTATTACCTCTCCCATGACGGGCGGCGC  
TTCCACAGGGCCTGCCGCTGGTGCATGACTTCACAGACGCTGTCATCCGGGAGCGGCGTCG  
CACCTCCCCACTCAGGGTATTGATGATTTTTTCAAAGACAAAGCCAAGTCCAAGACTTTGG  
ATTTTCATTGATGTGCTTCTGCTGAGCAAGGATGAAGATGGGAAGGCATTGTCAGATGAGGAT  
ATAAGAGCAGAGGCTGACACCTTCATGTTTGGAGGCCATGACACCACGGCCAGTGGCCTCTC  
CTGGGTCCTGTACAACCTTGCGAGGCACCCAGAATACCAGGAGCGCTGCCGACAGGAGGTGC  
AAGAGCTTCTGAAGGACCGCGATCCTAAAGAGATTGAATGGGACGACCTGGCCCAGCTGCCC  
TTCCTGACCATGTGCGTGAAGGAGAGCCTGAGGTTACATCCCCCAGCTCCCTTCATCTCCCG  
ATGCTGCACCCAGGACATTGTTCTCCCAGATGGCCGAGTCATCCCCAAAGGCATTACCTGCC  
TCATCGATATTATAGGGGTCCATCACAACCCAACCTGTGTGGCCGGATCCTGAGGTCTACGAC  
CCCTTCCGCTTTGACCCAGAGAACAGCAAGGGGAGGTCACCTCTGGCTTTTATTCTTTCTC  
CGCAGGGCCCAGGAACTGCATCGGGCAGGCGTTCGCCATGGCGGAGATGAAAGTGGTCCTGG  
CGTTGATGCTGCTGCACTTCCGGTTCCTGCCAGACCACACTGAGCCCCGCAGGAAGCTGGAA  
TTGATCATGCGCGCCGAGGGCGGGCTTTGGCTGCGGGTGGAGCCCCTGAATGTAGGCTTGCA  
GTGACTTTCTGACCCATCCACCTGTTTTTTTGCAGATTGTCATGAATAAAACGGTGCTGTCAA



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**FIGURE 182**

MSLLSLPWLGLRPVAMSPWLLLLLVVGSWLLARILAWTYAFYNNCRRLQCFPQPPKRNWFWG  
HLGLITPTEEGLKDSTQMSATYSQGFTVWLGPPIPFIVLCHPDTIRSITNASAAIAPKDNLF  
IRFLKPWLGEIGILLSGGDKWSRHRRLTPAFHFNILKSYITIFNKSANIMLDKWQHLASEGS  
SRLDMFEHISLMTLDSLQKCIFSFDSHCQERPSEYIATILELSALVEKRSQHILQHMDFLYY  
LSHDGRRFHRACRLVHDFDTDAVIRERRRTLPTQGIDDFKDKAKSKTLDFIDVLLLSKDEDG  
KALSDEDIRAEADTFMFGGHDTTASGLSWVLYNLARHPEYQERCQEVQELLKDRDPKEIEW  
DDLAQLPFLTMCVKESLRLHPPAPFISRCCTQDIVLPDGRVIPKGITCLIDIIGVHHNPTVW  
PDPEVYDPFRFDPENSKGRSPLAFIPFSAGPRNCIGQAFAMAEMKVVLALMLLHFRFLPDHT  
EPRRKLELIMRAEGGLWLRVEPLNVGLQ

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**FIGURE 183**

CAACAGAAGCCAAGAAGGAAGCCGTCTATCTTGTGGCGATCATGTATAAGCTGGCCTCCTGC  
TGTTTGCTTTTCACAGGATTCTTAAATCCTCTCTTATCTCTTCCTCTCCTTGACTCCAGGGA  
AATATCCTTTCAACTCTCAGCACCTCATGAAGACGCGCGCTTAACTCCGGAGGAGCTAGAAA  
GAGCTTCCCTTCTACAGATATTGCCAGAGATGCTGGGTGCAGAAAGAGGGGATATTCTCAGG  
AAAGCAGACTCAAGTACCAACATTTTTTAACCCAAGAGGAAATTTGAGAAAGTTTCAGGATTT  
CTCTGGACAAGATCCTAACATTTTACTGAGTCATCTTTTGGCCAGAATCTGGAAACCATACA  
AGAAACGTGAGACTCCTGATTGCTTCTGGAAATACTGTGTCTGAAGTGAAATAAGCATCTGT  
TAGTCAGCTCAGAAACACCCATCTTAGAATATGAAAAATAACACAATGCTTGATTTGAAAAC  
AGTGTGGAGAAAACTAGGCAAACCTACACCCTGTTTCATTGTTACCTGGAAAATAAATCCTCT  
ATGTTTTGCACAAAAA

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**FIGURE 184**

MYKLASCCLLFTGFLNPLLSLPLLLDSREISFQLSAPHEDARLTPEELERASLLQILPEMLGA

ERGDILRKADSSTNIFNPRGNLRKFQDFSGQDPNILLSHLLARIWKPYKKRETPDCFWKYCV

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**FIGURE 185**

GAACATTTT TAGTTCCCAAGGAATGTACATCAGCCCCACGGAAGCTAGGCCACCTCTGGGAT  
GGGGTTGCTGGTTTAAAACAAACGCCAGTCATCCTATATAAGGACCTGACAGCCACCAGGCA  
CCACCTCCGCCAGGAAGTGCAGGCCACCTGTCTGCAACCCAGCTGAGGCCATGCCCTCCCC  
AGGGACCGTCTGCAGCCTCCTGCTCCTCGGCATGCTCTGGCTGGACTTGGCCATGGCAGGCT  
CCAGCTTCCTGAGCCCTGAACACCAGAGAGTCCAGCAGAGAAAGGAGTCGAAGAAGCCACCA  
GCCAAGCTGCAGCCCCGAGCTCTAGCAGGCTGGCTCCGCCCCGGAAGATGGAGGTCAAGCAGA  
AGGGGCAGAGGATGAACTGGAAGTCCGGTTCAACGCCCCCTTTGATGTTGGAATCAAGCTGT  
CAGGGGTT CAGTACCAGCAGCACAGCCAGGCCCTGGGGAAGTTTCTTCAGGACATCCTCTGG  
GAAGAGGCCAAAGAGGCCCCAGCCGACAAGTGATCGCCCACAAGCCTTACTCACCTCTCTCT  
AAGTTTAGAAGCGCTCATCTGGCTTTTCGCTTGCTTCTGCAGCAACTCCCACGACTGTTGTA  
CAAGCTCAGGAGGCGAATAAATGTTCAAAGTGTGTA



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**FIGURE 186**

MPSPGTVCSLLLLGMLWLDLAMAGSSFLSPEHQRVQQRKESKKPPAKLQPRALAGWLRPEDG  
GQAEGAEDELEVRFNAPFDVGIKLSGVQYQQHSQALGKFLQDILWEEAKEAPADKO

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**FIGURE 187**

CGGCCACAGCTGGCATGCTCTGCCTGATCGCCATCCTGCTGTATGTCCTCGTCCAGTACCTC  
GTGAACCCCGGGGTGCTCCGCACGGACCCAGATGTCAAGAATATGAACACGTGGCTGCTGT  
TCCTCCCCCTGTTCCCGGTGCAGGTGCAGACCCTGATAGTCGTGATCATCGGGATGCTCGTG  
CTCCTGCTGGACTTTCTTGGCTTGGTGCACCTGGGCCAGCTGCTCATCTTCCACATCTACCT  
GAGTATGTCCCCACCCTAAGCCCCCGATCCCCCAAGGCTGGGTGGTCAGAGCTGCTCATC  
TTACACCTCTACTTGAGTATGTCCCTAACCCTGAGCCCCCACGCCTGGGGCCAGAGTCTTT  
GTCCCCCGTGTGCGCATGTGTTTCAGGGTCAGCCTCTCCAGAAGTGAGATCATGGACAAAAA  
GGGCAAATCACAGGAAGAAATTAAATCCATGAGGACCCAGCAGGCCAGCAAGAAGCTGAAC  
TCACGCCGAGACCTGCAGGAGTGGTGCCAGGTGCTTGAAGTAACAAGTTTAAAATGTTTCAGA  
GACAATGGAATGGAATCTATTAGGCAAGAACAGGACATTATGAAATAAGGACAGGTGGACTT  
CCAAAAACACAAGTAGAAATTCTAACAATGAAATATATTACAGGCAGGTACCCACTAACCA  
AACAACTGAAGCGAGAGCTGTGGTCTTGCTTGGTCTCACAGTGGGCACAGCGGTAGGCGGTC  
AGTCATGTTGCTGAACGACGGAGGGTAAACTCCCCAGCCCCAAGAAAACCTGTGTTGGAAGT  
AACAAACAACCTCCCTGCTCCTGGCACCAGCCGTTTTTGGTCATGGTGGGCCAGCTGCAAAGCG  
TCTTCCATTCTCTGGGCAGTGGTGGCCCCGAGGCTGTGGCCTCTCAGGGGGTTTCTGTGGAC  
ACGGGCAGCAGAGTGTGTCCAGGCCAGCCCCAAGAATGCCCTGCTCCTGACAGCTTGGCCA  
ACCCCTGGTCAGGGCAGAGGGAGTTGGGTGGGTGAGGCTCTGGGCTCACCTCCATCTCCAGA  
GCATCCCCTGCCTGCAGTTGTGGCAAGAACGCCAGCTCAGAATGAACACACCCCCACCAAGA  
GCCTCCTTGTTTCATAACCACAGGTTACCCTACAAACCACTGTCCCCACACAACCCTGGGGAT  
GTTTTTAAACACACACCTCTAACGCATATCTTACAGTCACTGTTGTCTTGCCTGAGGGTTGA  
ATTTTTTTTAAATGAAAGTGCAATGAAAATCACTGGATTAAATCCTACGGACACAGAGCTGAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 188**

MNTWLLFLPLFPVQVQTLIVVIIGMLVLLLDLGLVHLGQLLIFHIYLSMSPTLSPRSPQGW  
VVRAAHLTPLLEYVPNPEPPTPGARVFVPRVRMCSGSASPRSEIMDKKGKSQEEIKSMRTQQ  
AQQEAELTPRPAGVVPGA

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**FIGURE 189**

GGAGTGCAGATGGCATCCTTCGGTTCTTCCAGACAAGCTGCAAGACGCTGACCATGGCCAAG  
ATGGAGCTCTCGAAGGCCTTCTCTGGCCAGCGGACACTCCTATCTGCCATCCTCAGCATGCT  
ATCACTCAGCTTCTCCACAACATCCCTGCTCAGCAACTACTGGTTTGTGGGCACACAGAAGG  
TGCCCAAGCCCCTGTGCGAGAAAGGTCTGGCAGCCAAGTGCTTTGACATGCCAGTGTCCCTG  
GATGGAGATACCAACACATCCACCCAGGAGGTGGTACAATACTGGGAGACTGGGGATGA  
CCGGTTCTCCTTCCGGAGCTTCCGGAGTGGCATGTGGCTATCCTGTGAGGAACTGTGGAAG  
AACCAGGGGAGAGGTGCCGAAGTTTCATTGAACTTACACCACCAGCCAAGAGAGGTGAGAAA  
GGACTACTGGAATTTGCCACGTTGCAAGGCCCATGTCACCCCACTCTCCGATTTGGAGGGAA  
GCGGTTGATGGAGAAGGCTTCCCTCCCCTCCCCTCCCTTGGGGCTTTGTGGCAAAAATCCTA  
TGGTTATCCCTGGGAACGCAGATCACCTACATCGGACTTCAATTCATCAGCTTCCTCCTGCT  
ACTAACAGACTTGCTACTCACTGGGAACCCTGCCTGTGGGCTCAAACCTGAGCGCCTTTGCTG  
CTGTTTCCTCTGTCCTGTCAGGTCTCCTGGGGATGGTGGCCCACATGATGTATTCAACAAGTC  
TTCCAAGCGACTGTCAACTTGGGTCCAGAAGACTGGAGACCACATGTTTGAATTATGGCTG  
GGCCTTCTACATGGCCTGGCTCTCCTTCACCTGCTGCATGGCGTCGGCTGTCACCACCTTCA  
ACACGTACACCAGGATGGTGCTGGAGTTCAAGTGCAAGCATAGTAAGAGCTTCAAGGAAAAC  
CCGAACCTGCCTACCACATCACCATCAGTGTTTCCCTCGGCGGCTGTCAAGTGCAGCCCCAC  
CGTGGGTCCTTTGACCAGCTACCACCAGTATCATAATCAGCCCATCCACTCTGTCTCTGAGG  
GAGTCGACTTCTACTCCGAGCTGCGGAACAAGGGATTTCAAAGAGGGGCCAGCCAGGAGCTG  
AAAGAAGCAGTTAGGTCATCTGTAGAGGAAGAGCAGTGTTAGGAGTTAAGCGGGTTTGGGGA  
GTAGGCTTGAGCCCTACCTTACACGTCTGCTGATTATCAACATGTGCTTAAGCCAACATCCG  
TCTCTTGAGCATGGTTTTTTAGAGGCTACGAATAAGGCTATGAATAAGGGTTATCTTTAAGTC  
CTAAGGGATTCTGGGTGCCACTGCTCTCTTTTCTCTACAGCTCCATCTTGTTTCACCCAC  
CCCACATCTCACACATCCAGAATTCCCTTCTTTACTGATAGTTTCTGTGCCAGGTTCTGGGC  
TAAACCATGGAGATAAAAAGAAGAGTAAAATACACTTCCCGACCTTAAGGATCTGAAA



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**FIGURE 190**

MAKMELSKAFSGQRTLLSAILSMLSLSFSTTSLLSNYWFVGTQKVPKPLCEKGLAAKCFDMP  
VSLDGDNTNTSTQEVVQYNWETGDDRF SFRSFRSGMWLSCEETVEEPGERCRSFIELTPPAKR  
GEKGLLEFATLQGPCHPTLRFGGKRLMEKASLPSPPLGLCGKNPMVIPGNADHLHRTSIHQL  
PPATNRLATHWEPCLWAQTERLCCCFLCPVRSPGDGGPHDVFTSLPSPDCQLGSRRLCTTCLE  
LWLGLLHGLALLHLLHGVGCHHLQHVVHODGAGVQVQA

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**FIGURE 191**

AACTGGAAGGAAAGAAAGAAAGGTCAGCTTTGGCCCAGATGTGGTTACCCCTTGGTCTCCTG  
TCTTTATGTCTTTCTCCTCTTCCTATTCTGTCACTCTCCCTCACTTAAGTCTCAGGCCTGTCA  
GCAGCTCCTGTGGACATTGCCATCCCCTCTGGTAGCCTTCAGAGCAAACAGGACAACCTATG  
TTATGGATGTTTCCACCAACCAGGGTAGTGGCATGGAGCACCGTAACCATCTGTGCTTCTGT  
GATCTCTATGACAGAGCCACTTCTCCACCTCTGAAATGTTCCCTGCTCTGAAATCTGGCATG  
AGATGGCACAGGTGACCACGCAGAAGCCACCAGAATCTTGCCTGCCCTATTCCTCCTCCCAA  
GTCTGTTCTCTTATTGTCAACCTCAGCACAACAGGCTGGCGCCAATGGCATTACAGAGAAAG  
CAATCTGTGTGGCTAGTGGGCAGATTACCATGCAAGCCCCAGGAGAAATGGAGGAGCTTTGT  
AGCCACCTCCCTGTCAGCCAGTATTAACATGTCCCCTTCCCCCTGCCCCGCCGTAGATTGAG  
GACATTCGCCCCCTGTGTGCCACCAAACCAGGACTTTCCCCTTGGCTTGGCATCCCTGGCTCT  
CTCCTGGTACCCAGCAAGACGTCTGTTCCAGGGCAGTGTAGCATCTTTCAAGCTCCGTTACT  
ATGGCGATGGCCATGATGTTACAATCCCCTTGCCTGAATAATCAAGTGGGAAGGGGAAGCA  
GAGGGAAATGGGGCCATGTGAATGCAGCTGCTCTGTTCTCCCTACCCTGAGGAAAAACCAAA  
GGGAAGCAACAGGAACTTCTGCAACTGGTTTTTATCGGAAAGATCATCCTGCCTGCAGATGC  
TGTTGAAGGGGCACAAGAAATGTAGCTGGAGAAGATTGATGAAAGTGCAGGTGTGTAAGGAA  
ATAGAACAGTCTGCTGGGAGTCAGACCTGGAATTCTGATTCCAACTCTTTATTACTTTGGG  
AAGTCACTCAGCCTCCCCGTAGCCATCTCCAGGGTGACGGAACCCAGTGTATTACCTGCTGG  
AACCAAGGAACTAACAATGTAGGTTACTAGTGAATACCCCAATGGTTTCTCCAATTATGCC  
CATGCCACCAAAACAATAAAACAAAATTCTCTAACACTGAAA

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**FIGURE 192**

MWLPLGLLSLCLSPILSSPSLKSQACQQLLWTLPSPLVAFRANRTTYVMDVSTNQSGME

HRNHLCFCDLYDRATSPPLKCSLL

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**FIGURE 193**

GTAGCGCGTCTTGGGTCTCCCGGCTGCCGCTGCTGCCGCCGCCGCTCGGGTCTGAGGCCA  
GGAGCGACGTCAACGCCATGGCAGGCATCAAAGCTTTGATTAGTTTGTCTTTGGAGGAGCA  
ATCGGACTGATGTTTTTTGATGCTTGGATGTGCCCTTCCAATATACAACAATACTGGCCCCCT  
CTTTGTTCTATTTTTTTTACATCCTTTACCTATTCCATACTGCATAGCAAGAAGATTAGTGG  
ATGATACAGATGCTATGAGTAACGCTTGTAAGGAAGTTGCCATCTTTCTTACAACGGGCATT  
GTCGTGTCAGCTTTTGGACTCCCTATTGTATTTGCCAGAGCACATCTGATTGAGTGGGGAGC  
TTGTGCACTTGTTCTCACAGGAAACACAGTCATCTTTGCAACTATACTAGGCTTTTTCTTGG  
TCTTTGGAAGCAATGACGACTTCAGCTGGCAGCAGTGGTGAAGAAAGAAATTAAGTAATG  
TCAAATGGACTTCCTGTCATTTGTTGGCCATTACCGCACACAGGAGATGGGGCAGTTAATGC  
TGAATGGTATAGCAAGCCTCTTGGGGGTATTTTAGGTGCTCCCTTCTCACTTTTATTGTAAG  
CATACTATTTTTCACAGAGACTTGCTGAAGGATTAAAAGGATTTTCTCTTTTGGAAAAGCTTG  
ACTGATTTTCACACTTATCTATAGTATGCTTTTTTGTGGTGTCTGCTGAATTTAAATATTTAT  
GTGTTTTTCTGTTAGGTTGATTTTTTTTTTGGAAATCAATATGCAATGTTAAACACTTTTTTAA  
TGTAATCATTTGCATTGGTTAGGAATTCAGAATTCGCGCCGGCTCTATTACTGGTCAAGTACA  
TCTTTTCTCTTAAATTAATTTAGCCTCCATTATTACAAAAAATTATAAAAAATAAGTTTTTCAG  
TCAGTCAGGATGACATCACTCCCAATGTTATGCAGACATACAGACGGTTGGCATAACGTTATA  
GACTGTATACTCAGTGCAAATATAGCTGCATTTTATACCTCAGAGGGGCCAAGTGTTAATGCC  
CATGCCCTCCGTTAAGGGTTGTTGGTTTTACTGGTAGACAGATGTTTTGTGGATTGAAAATT  
ATTTTATGGAATTGCTACAGAGGAGTGCTTTTCTTCTCAATTGTTAGAAGAATTTATGTTAA  
ACTTTAAGGTAAGGGTGTAACAAACATTTTTTGAGATAAGGTTTTTATTTATGTTTATTATTGT  
TAGAGTGAGTTGCAATGTGGGAAGAAATGACATTGAAATTCAGTTTTTGAATCCTGTTTCT  
ATTTATAAGTGAAATTTGTGATCTCCTATCAACCTTTCATGTTTTACCCTGTTAAATGGAC  
ATACATGGAACCACTACTGATGAGGGACAGTTGTATGTTTGCATCATATATGCCAGAAAACC  
TTCCTCTGCTTCCTCCTTTTGACTTATTTGGTATGTTGTATATATTACATAAAATAACTTTT  
CAAATATAGTTTAAATAACACTTAGAAGTGTTTACTTACCTGGAAAATAATTGCTATGCCGTA  
CATTACAGAGTGCCCCCTCCCTGCAAGGCCTTGCCATGATTAACAAGTAAGTTGTTAGTCTT  
ACAGATAATTCATGCATTAACAGTTTAAGATTTAGACCATGGTAATAGTAGTTCTTATTCTC  
TAAGGTTATATCATATGTAATTTAAAAGTATTTTTTAAGACAAGTTTCCTGTATACCTCTGAA  
CTGTTTTTGATTTTGAGTTCATCATGATAGATCTGCTGTTTCCTTATAAAAGGCATTTGTTGT  
GTGAGTTAATGCAAAGTAGCCAAGTCCAGCTATATAGCAGCTTCAGAAACATACCTGACCAA  
AAAATTCCCAGTAACCAGGCATGATCAATTTATAGTGGTCGTTTACATCTAATAATTATCAG  
GACTTTTTTTCAGGAGTGGGTTATAAAAAACATTCAAGTTGGTCTGACAGTATTTTTGTTAAGGA  
TATTTGTTTGTATGTTTATTCAGTATACTTACATAAAAAATTATTTGCGCCATCAGCCAAAAC  
CAGTAATCATGACAGCTGTCTGTTGTTTTATGAAGTTTATTTCTCAAGAAAATGGGAATAAA  
TTTGGGATTTGTTTCAGCTTTTTTTTACTAAAGATGCCTAAAGCCACAGGTTTTTATTGCCTAACT  
TAAGCCATGACTTTTAGATATGAGATGACGGGAAGCAGGACGAAATATCGGCGTGTGGCTGG  
AGCCTTCCCCTGGAGGCTGAAAGTGGCTTGTGGTATTATAATGTTTCAGATTTCAAGAGGAA  
GGTGCAGGTACACATGAGTTAGAGAGCTGGTGAGACAGTTGGGAAGTCTTTGTGCTTGTGAT  
CTACTGGACTTTTTTTTTTGCAGGAAGTGCATTCTCTGGTCCCTCCCTATTTTCTGTTCTGGA  
TGTCAGTGCAGTGCATGCTACTGTTTTATCCACTTGGCCACAGACTTTTTCTAACAGCTGC  
GTATTATTTCTATATACTAATTGCATTGGCAGCATTGTGTCTTTGACCTTGTATACTAGCTT  
GACATAGTGCTGTCTCTGATTTCTAGGCTAGTTACTTGAGATATGAATTTTCCATAGAATAT  
GCACTGATACAACATTACCATTTCTTCTATGGAAAGAAACTTTTGATGATGAAACAATAAAG  
ATTTTAAATATCTATTTTAAAAAATAA



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**FIGURE 194**

MAGIKALISLSFGGAIGLMFLMLGCALPIYNKYWPLFVLFFYILSPIPYCIARRLVDDTDAM  
SNACKELAIFLTGTGIVVSAFGLPIVFARAHLEWGACALVLTGNTVIFATILGFFLVFGSND  
DFSWQQW

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**FIGURE 195A**

CCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCC  
CACGCGTCCGCCCACGCGTCCGGTGCAAGCTCGCGCCGCACACTGCCTGGTGGAGGGAAGGA  
GCCCCGGGCGCCTCTCGCCGCTCCCCGCGCCGCGTCCGCACCTCCCCACCGCCCGCCGCCCG  
CCGCCCCGCGCCCGCAAAGCATGAGTGAGCCCCGCTCTCTGCAGCTGCCCCGGGGCGCGAATGG  
CAGGCTGTTTCCGCGGAGTAAAAGGTGGCGCCGGTCAGTGGTCTTTCCAATGACGGACATT  
AACCAGACTGTCAGATCCTGGGGAGTCGCGAGCCCCGAGTTTGGAGTTTTTTCCCCCACA  
CGTCACAGTCCGAACCTGCAGAGGGAAAGGAAGGCGGCAGGAAGGCGAAGCTCGGGCTCCGGC  
ACGTAGTTGGGAAACTTGCGGGTCCTAGAAGTCGCTCCCCGCTTGCCGGCCGCCCTTGCA  
GCCCCGAGCCGAGCAGCAAAGTGAGACATTGTGCGCCTGCCAGATCCGCCGGCCGCGGACCG  
GGGCTGCCTCGGAAACACAGAGGGGTCTTCTCTCGCCCTGCATATAATTAGCCTGCACACAA  
AGGGAGCAGCTGAATGGAGGTGTCACTCTCTGGAAAAGGATTTCTGACCGAGCGCTTCCAA  
TGGACATTCTCCAGTCTCTCTGGAAAGATTCTCGCTAATGGATTTCCTGCTGCTCGGTCTCT  
GTCTATACTGGCTGCTGAGGAGGCCCTCGGGGGTGGTCTTGTGTCTGCTGGGGGCCTGCTTT  
CAGATGCTGCCCCGCCGCCCCAGCGGGTGCCCGCAGCTGTGCCGGTGCGAGGGGCGGCTGCT  
GTACTGCGAGGCGCTCAACCTCACCGAGGCGCCCCACAACCTGTCCGGCCTGCTGGGCTTGT  
CCCTGCGCTACAACAGCCTCTCGGAGCTGCGCGCCGGCCAGTTCACGGGGTTAATGCAGCTC  
ACGTGGCTCTATCTGGATCACAATCACATCTGCTCCGTGCAGGGGGACGCCTTTCAGAACT  
GCGCCGAGTTAAGGAACTCACGCTGAGTTCCAACAGATCACCCAACCTGCCCAACACCACCT  
TCCGGCCCATGCCCAACCTGCGCAGCGTGGACCTCTCGTACAACAAGCTGCAGGCGCTCGCG  
CCCGACCTCTTCCACGGGCTGCGGAAGCTCACCACGCTGCATATGCGGGCCAACGCCATCCA  
GTTTGTGCCCCGTGCGCATCTTCCAGGACTGCCGCAGCCTCAAGTTTCTCGACATCGGATACA  
ATCAGCTCAAGAGTCTGGCGCGCAACTCTTTCGCCGGCTTGTTTAAGCTCACCGAGCTGCAC  
CTCGAGCACAACGACTTGGTCAAGGTGAACTTCGCCCACTTCCCGCGCCTCATCTCCCTGCA  
CTCGCTCTGCCTGCGGAGGAACAAGGTGGCCATTGTGGTCAGCTCGCTGGACTGGGTTTGGA  
ACCTGGAGAAAATGGACTTGTGCGGGCAACGAGATCGAGTACATGGAGCCCCATGTGTTGAG  
ACCGTGCCGCACCTGCAGTCCCTGCAGCTGGACTCCAACCGCCTCACCTACATCGAGCCCCG  
GATCCTCAACTCTTGAAGTCCCTGACAAGCATCACCTGGCCGGGAACCTGTGGGATTGCG  
GGCGCAACGTGTGTGCCCTAGCCTCGTGGCTCAGCAACTTCCAGGGGCGCTACGATGGCAAC  
TTGCAGTGCGCCAGCCCGAGTACGCACAGGGCGAGGACGTCCTGGACGCCGTGTACGCCTT  
CCACCTGTGCGAGGATGGGGCCGAGCCCAACAGCGGCCACCTGCTCTCGGCCGTACCAACC  
GCAGTGATCTGGGGCCCCCTGCCAGCTCGGCCACCACGCTCGCGGACGGCGGGGAGGGGCAG  
CACGACGGCACATTCGAGCCTGCCACCGTGGCTCTTCCAGGCGGCGAGCACGCCGAGAACGC  
CGTGACAGATCCACAAGGTGGTCACGGGCACCATGGCCCTCATCTTCTCCTTCTCATCGTGG  
TCCTGGTGCTCTACGTGTCCTGGAAGTGTTTCCCAGCCAGCCTCAGGCAGCTCAGACAGTGC  
TTTGTACGCGAGCGCAGGAAGCAAAGCAGAAACAGACCATGCATCAGATGGCTGCCATGTC  
TGCCAGGAATACTACGTTGATTACAAACCGAACCACATTGAGGGAGCCCTGGTGATCATCA  
ACGAGTATGGCTCGTGTACCTGCCACCAGCAGCCCGCGAGGGAATGCGAGGTGTGATTGTCC  
CAGTGGCTCTCAACCCATGCGCTACCAAATACGCCTGGGCAGCCGGGACGGGCCGGCGGGCA  
CCAGGCTGGGGTCTCCTTGTCTGTGCTCTGATATGCTCCTTGACTGAACTTTAAGGGGATC  
TCTCCCAGAGACTTGACATTTTAGCTTTATTGTGTCTTAAAAACAAAAGCGAATTAACAC  
AACAAAAAACCACCCACCCACAACCTTCAGGACAGTCTATCTTAAATTTTCATATGAGAACTCC  
TTCCTCCCTTTGAAGATCTGTCCATATTCAGGAATCTGAGAGTGTAAGAAAGGTGGCCATAA  
GACAGAGAGAGAATAATCGTGCTTTGTTTTATGCTACTCCTCCCACCCTGCCCATGATTAAA  
CATCATGTATGTAGAAGATCTTAAGTCCATACGCATTTTCATGAAGAACCATTGGAAAGAGGA  
ATCTGCAATCTGGGAGCTTAAGAGCAAATGATGACCATAGAAAGCTATGTTCTTACTTTGTG  
TGTGTGTCTGTATGTTTCTGCGTTGTGTGTCTTTGTAGGCAAGCAAACGTTGTCTACACAAA  
CGGGAATTTAGCTCACATCATTTTCATGCCCTGTGCCTCTAGCTCTGGAGATTGGTGGGGGG  
AGGTGGGGGGGAAACGGCAGGAATAAGGGAAAGTGGTAGTTTTAACTAAGGTTTTGTAACT  
TGAAATCTTTCTTTCTCAAATTAATTATCTTTAAGCTTCAAGAACTTGCTCTGACCCCTC  
TAAGCAAACCTACTAAGCATTTTAAAGAGAATCTAATTTTAAAGGTGTAGCACCTTTTTTT  
TATTCTTCCCACAGAGGGTGCTAATCTCATTATGCTGTGCTATCTGAAAAGAACTTAAGGCC  
ACAATTCACGTCTCGTCCTGGGCATTGTGATGGATTGACCCCTGCATTTGCAGTACCTTCCCA  
GCTGATTAAAGTTCAGCAGTGGTATTGAGGTTTTTCGAATATTTATATAGAAAAAAGTCTT  
TTCACATGACAAATGACACTCTCACACCAGTCTTAGCCCTAGTAGTTTTTTAGGTTGGACCA  
GAGGAAGCAGGTTAAATGAGACCTGTCCTCTGCTGCACTCAGAAAAAATAGGCAGTCCCTGA  
TGCTCAGATCTTAGCCTTGATATTAATAGTTGAGACCACCTACCCACAATGCAGCCTATACT  
CCCAAGACTACAAAGTTACCATCGCAAAGGAAAGGTTATTCCAGTAAAAGGAAATAGTTTTCT  
TCAACCATTTAAAAATATTCTTCTGAACTCATCAAAGTAGAAGAGCCCCAACCTTTTCTCT  
CTGCCTTCAAGAAGGCAGACATTTGGTATGATTTAGCATCAACAACACATTTATGAGTATAT

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**FIGURE 195B**

GTAAGTAATCAGAGGGGCAAATGCCACTTGTTATTCCTCCCAAGTTTTCCAAGCAAGTACAC  
ACAGATCTCTGGTAGGATTAGGGGCCACTTGTGTTTCCGGCTTATTTTAGTCGACTTGTCAG  
CAAGTTTGATGCCTAGTCTATCTGACATGGCCCAGTAGAACAGGGCATTGATGGATCACATG  
AGATGGTAGAAGGAACATCATCACATACCCCTCTCACAGAGAAAATTATCAAAGAACCAGAA  
ATTATATCTGTTTTGGAGCAAGAGTGTCTAATGTTTCAGGGTAGTCAAAATAAACATAAAT  
TATCTCCTCTAGATGAGTGGCGATGTTGGCTGATTTGGGTCTGCCATTGACAGAATGTCAA  
TAAAAAGGAATTAGCTAGAATATGACCATTAAATGTGCTTCTGAAATATATTTTGAGATAGG  
TTTAGAATGTCA

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**FIGURE 196**

MDFLLLGLCLYWLLRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEAPH  
NLSGLLGLSLRYNSLSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTLSSNQ  
ITQLPNTTFRPMPNLRSDLSYNKLQALAPDLFHGLRKLTTLHMRANAIQFVPVRIFQDCRS  
LKFLDIGYNQLKSLARNSFAGLFKLTEHLHLEHNDLVKVNFAHFPRLLSLHSLCLRRNKVAIV  
VSSLDWVWNLEKMDLSGNEIEYMEPHVFETVPHLQSLQLDSNRLTYIEPRILNSWKSITSIT  
LAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDVYAFHLCEDGAEPTSG  
HLLSAVTNRSDLGPPASSATTLADGGEGQHDGTFEPATVALPGGEHAENAVQIHKVVTGTMA  
LIFSFLIVVLVLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQMAAMSAQEYYVDYKPNH  
IEGALVIINEYGSCTCHQQPARECEV



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**FIGURE 197**

GTGCAAGGAGCCGAGGCGAGATGGGCGTCCTGGGCGGGTCCTGCTGTGGCTGCAGCTCTGC  
GCACTGACCCAGGCGGTCTCCAAACTCTGGGTCCCCAACACGGACTTCGACGTCGCAGCCAA  
CTGGAGCCAGAACCGGACCCCGTGCGCCGGCGGGCGCCGTTGAGTTCCCGGCGGACAAGATGG  
TGTCAGTCCTGGTGCAAGAAGGTCACGCCGTCTCAGACATGCTCCTGCCGCTGGATGGGGAA  
CTCGTCCTGGCTTCAGGAGCCGGATTCTGGCGTCTCAGACGTGGGCTCGCACCTGGACTGTGG  
CGCGGGCGAACCTGCCGTCTTCCGCGACTCTGACCGCTTCTCCTGGCATGACCCGCACCTGT  
GGCGCTCTGGGGACGAGGCACCTGGCCTCTTCTTCGTGGACGCCGAGCGCGTGCCCTGCCGC  
CACGACGACGTCTTCTTTCCGCCTAGTGCCCTCCTTCCGCGTGGGGCTCGGCCCTGGCGCTAG  
CCCCGTGCGTGTCCGCAGCATCTCGGCTCTGGGCCGGACGTTACGCGCGACGAGGACCTGG  
CTGTTTTCTCTGGCGTCCCGCGCGGGCCGCCTACGCTTCCACGGGCCGGGCGCGCTGAGCGTG  
GGCCCCGAGGACTGCGCGGACCCGTCGGGCTGCGTCTGCGGCAACGCGGAGGCGCAGCCGTG  
GATCTGCGCGGCCCTGCTCCAGCCCCCT

**FIGURE 198**

MGVLGRVLLWLQLCALTQAVSKLWVPNTDFDVAANWSQNRTPCAGGAVEFPADKMVSVLVQE  
GHAUSDMLLPLDGELVLASGAGFGVSDVGSHLDCGAGEPAVFRDSDRFSWHDPHLWRSIDEA  
PGLFFVDAERVPCRHDDVFFPPSASFRVGLGPGASPVRVRSISALGRTFTRDEDLAVFLASR  
AGRLRFHGPGLSVGPEDCADPSGCVCGNAEAQPWICAALLQP

[illegible]

**FIGURE 200**

MGPVKQLKRMFEPTRLIATIMVLLCFALTLCSAFWWHNKGLALIFCILQSLALTWYSLSFIP  
FARDAVKKCFVCLA



**FIGURE 201**

TTGAGCGCAGGTGAGCTCCTGCGCGTTCCGGGGGCGTTCCTCCAGTCACCCTCCCGCCGTTA  
CCCGCGGCGCGCCCGAGGGAGTCTCCTCCAGACCCTCCCTCCCGTTGCTCCAAACTAATACG  
GACTGAACGGATCGCTGCGAGGGTGGGAGAGAAAATTAGGGGGAGAAAGGACAGAGAGAGCA  
ACTACCATCCATAGCCAGATAGATTATCTTACACTGAACTGATCAAGTACTTTGAAAATGAC  
TTCGAAATTTATCTTGGTGTCTTTCATACTTGCTGCACTGAGTCTTCAACCACCTTTTCTC  
TCCAAC TAGACCAGCAAAAGGTTCTACTAGTTTCTTTTGATGGATTCCGTTGGGATTACTTA  
TATAAAGTTCCAACGCCCCATTTTCATTATATTATGAAATATGGTGTTACGTGAAGCAAGT  
TACTAATGTTTTTATTACAAAACCTACCCTAACCATTAATACTTTGGTAACCTGGCCTCTTTG  
CAGAGAATCATGGGATTGTTGCAAATGATATGTTTGATCCTATTCGGAACAAATCTTTCTCC  
TTGGATCACATGAATATTTATGATTCCAAGTTTTGGGAAGAAGCGACACCAATATGGATCAC  
AAACCAGAGGGCAGGACATACTAGTGGTGCAGCCATGTGGCCCCGGAACAGATGTAAAAATAC  
ATAAGCGCTTTCCTACTCATTACATGCCTTACAATGAGTCAGTTTCATTTGAAGATAGAGTT  
GCCAAAATTGTTGAATGGTTTACGTCAAAAGAGCCCATAAATCTTGGTCTTCTCTATTGGGA  
AGACCCTGATGACATGGGCCACCATTTGGGACCTGACAGTCCGCTCATGGGGCCTGTCATTT  
CAGATATTGACAAGAAGTTAGGATATCTCATACAAATGCTGAAAAAGGCAAAGTTGTGGAAC  
ACTCTGAACCTAATCATCACAAGTGATCATGGAATGACGCAGTGCTCTGAGGAAAGGTTAAT  
AGAACTTGACCAGTACCTGGATAAAGACCACTATAACCCTGATTGATCAATCTCCAGTAGCAG  
CCATCTTGCCAAAAGAAGGTAAATTTGATGAAGTCTATGAAGCACTAACTCACGCTCATCCT  
AATCTTACTGTTTACAAAAAGAAGACGTTCCAGAAAGGTGGCATTACAAATACAACAGTCG  
AATTCAACCAATCATAGCAGTGGCTGATGAAGGGTGGCACATTTTACAGAATAAGTCAGATG  
ACTTTCTGTTAGGCAACCACGGTTACGATAATGCGTTAGCAGATATGCATCCAATATTTTTA  
GCCCATGGTCCTGCCTTCAGAAAGAATTTCTCAAAGAAGCCATGAACTCCACAGATTTGTA  
CCCCTACTATGCCACCTCCTCAATATCACTGCCATGCCACACAATGGATCATTCTGGAATG  
TCCAGGATCTGCTCAATTCAGCAATGCCAAGGGTGGTCCCTTATACACAGAGTACTATACTC  
CTCCCTGGTAGTGTTAAACCAGCAGAATATGACCAAGAGGGGTCATACCCTTATTTTCATAGG  
GGTCTCTCTTGGCAGCATTATAGTGATTGTATTTTTTTGTAATTTTCATTAAGCATTTAATTC  
ACAGTCAAATACCTGCCTTACAAGATATGCATGCTGAAATAGCTCAACCATTATTACAAGCC  
**TAAT**GT TACTTTGAAGTGGATTTGCATATTGAAGTGGAGATTCCATAATTATGTCAGTGTTT  
AAAGGTTTCAAATTCTGGGAAACCAGTTCCAAACATCTGCAGAAACCATTAAAGCAGTTACAT  
ATTTAGGTATACACACACACACACACACATACACACACACGACCAAAATACTTACAC  
CTGCAAAGGAATAAAGATGTGAGAGTATGTCTCCATTGTTCACTGTAGCATAGGGATAGATA  
AGATCCTGCTTTATTTGGACTTGGCGCAGATAATGTATATATTTAGCAACTTTGCACTATGT  
AAAGTACCTTATATATTGCACTTTAAATTTCTCTCCTGATGGGTACTTTAATTTGAAATGCA  
CTTTATGGACAGTTATGTCTTATAACTTGATTGAAAATGACAACCTTTTGCACCCATGTCAC  
AGAATACTTGTTACGCATTGTTCAAACCTGAAGGAAATTTCTAATAATCCCGAATAATGAACA  
TAGAAATCTATCTCCATAAATTGAGAGAAGAAGAAGGTGATAAGTGTTGAAAATTAAATGTG  
ATAACCTTTGAACCTTGAATTTTGGAGATGTATTCCCAACAGCAGAATGCAACTGTGGGCAT  
TTCTTGTCCTTATTTCTTTCCAGAGAACGTGGTTTTTCATTTATTTTTCCCTCAAAGAGAGTC  
AAATACTGACAGATTCGTTCTAAATATATTGTTTCTGTCATAAAATTATTGTGATTTCTCTGA  
TGAGTCATATTACTGTGATTTTTCATAATAATGAAGACACCATGAATATACTTTTCTTCTATA  
TAGTTCAGCAATGGCCTGAATAGAAGCAACCAGGCACCATCTCAGCAATGTTTTCTCTTGTT  
TGTAATTATTTGCTCCTTTGAAAATTAAATCACTATTAATTACATTAAAAATCAAATTGGAT  
AAAAAAAAAAAAAAAAAAAA

**FIGURE 202**

MTSKFILVSFILAAALSLSTTFSLQLDQQKVLLVSFDGFRWDYLYKVPTPHFHYIMKYGVHVK  
QVTNVFITKTYPNHYTLVTGLFAENHGIVANDMFDPIRNKSFSLDHMNIYDSKFWEEATPIW  
ITNQRAGHTSGAAMWPGTDVKIHKRFP THYMPYNESVSFEDRVAKIVEWFTSKEPINLGLLY  
WEDPDDMGHHLGPDSPLMGPVISDIDKKLGYLIQMLKKAKLWNTLNLIITSDHGMTQCSEER  
LIELDQYLDKDHYTELIDQSPVAAILPKEGKFDEVYEALTHAHPNLTVYKKEDVPERWHYKYN  
SRIQPIIAVADEGWHILQNKSDDFLLGNHGYDNALADMHPIFLAHGPAFRKNFSKEAMNSTD  
LYPLLCHLLNITAMPHNGSFWNVQDLLNSAMPRVVPYTQSTILLPGSVKPAEYDQEGSYFYF  
IGVSLGSIIVIVFFVIFIKHLIHSQIPALQDMHAEIAQPLLQA

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**FIGURE 203**

GGATTTTTGTGATCCGCGATTCTGCTCCACGGGCGGGACCTTTGTAACTGCGGGAGGCCAG  
GACAGGCCACCTGCGGGGCGGGAGGCAGCCGGGGTGAGGGAGGTGAAGAAACCAAGACGC  
AGAGAGGCCAAGCCCCCTTGCCTTGGGTCACACAGCCAAAGGAGGCAGAGCCAGAACTCACAA  
CCAGATCCAGAGGCAACAGGGACATGGCCACCTGGGACGAAAAGGCAGTCACCCGCAGGGCC  
AAGGTGGCTCCCGCTGAGAGGATGAGCAAGTTCTTAAGGCACTTCACGGTCGTGGGAGACGA  
CTACCATGCCTGGAACATCAACTACAAGAAATGGGAGAATGAAGAGGAGGAGGAGGAGGAGG  
AGCAGCCACCACCCACACCAGTCTCAGGCGAGGAAGGCAGAGCTGCAGCCCCTGACGTTGCC  
CCTGCCCCCTGGCCCCGCACCCAGGGCCCCCCTTGACTTCAGGGGCATGTTGAGGAACTGTT  
CAGCTCCCACAGGTTTCAGGTCATCATCATCTGCTTGGTGGTTCTGGATGCCCTCCTGGTGC  
TTGCTGAGCTCATCCTGGACCTGAAGATCATCCAGCCCGACAAGAATAACTATGCTGCCATG  
GTATTCCACTACATGAGCATCACCATCTTGGTCTTTTTTTATGATGGAGATCATCTTTAAATT  
ATTTGTCTTCCGCCTGAGTTCTTTCACCACAAGTTTGAGATCCTGGATGCCCGTCGTGGTGG  
TGGTCTCATTATCCTGGACATTGTCCTCCTGTTCCAGGAGCACCAAGTTTGAGGCTCTGGGC  
CTGCTGATTCTGCTCCGGCTGTGGCGGGTGGCCCGGATCATCAATGGGATTATCATCTCAGT  
TAAGACACGTTTCAGAACGGCAACTCTTAAGGTAAAACAGATGAATGTACAATTGGCCGCCA  
AGATTCAACACCTTGAGTTCAGCTGCTCTGAGAAGCCCCTGGACTGATGAGTTTGCTGTATC  
AACCTGTAAGGAGAAGCTCTCTCCGGATGGCTATGGGAATGAAAGAATCCGACTTCTACTCT  
CACACAGCCACCGTGAAAGTCCTGGAGTAAAATGTGCTGTGTACAGAAGAGAGAGAAGGAAG  
CAGGCTGGCATGTTCACTGGGCTGGTGTACGACAGAGAACCTGACAGTCACTGGCCAGTTA  
TCACTTCAGATTACAAATCACACAGAGCATCTGCCTGTTTTCAATCACAAGAGAACAAAACC  
AAAATCTATAAAGATATTCTGAAAATATGACAGAATTTGACAAATAAAAGCATAAACGTGTA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 204**

MATWDEKAVTRRAKVAPAERMSKFLRHFTVVGDDYHAWNINYKKWENEEEEEEEEQPPPTPV  
SGEEGRAAAPDVAPAPGPAPRAPLDFRGMLRKLFSSHRFQVIIICLVVLDALLVLAELILDL  
KIIQPDKNNYAAMVFHYMSITILVFFMMEIIFKLFVFRLSSFTTSLRSWMPVVVVVSFILDI  
VLLFQEHQFEALGLLILLRLWRVARIINGIIISVKTRSERQLRLKQMNVLAAKIQHLEFS  
CSEKPLD



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**FIGURE 205**

CGGCTCGAGCTCGAGCCGAATCGGCTCGAGGGGCAGTGGAGCACCCAGCAGGCCGCCAACAT  
GCTCTGTCTGTGCCTGTACGTGCCGGTCATCGGGGAAGCCCAGACCGAGTTCAGTACTTTG  
AGTCGAAGGGGCTCCCTGCCGAGCTGAAGTCCATTTTCAAGCTCAGTGTCTTCATCCCCTCC  
CAGGAATTCTCCACCTACCGCCAGTGGGAAGCAGAAAATTGTACAAGCTGGAGATAAGGACCT  
TGATGGGCAGCTAGACTTTGAAGAATTTGTCCATTATCTCCAAGATCATGAGAAGAAGCTGA  
GGCTGGTGTTTAAGATTTTGGACAAAAAGAATGATGGACGCATTGACGCGCAGGAGATCATG  
CAGTCCCTGCCGGACTTGGGAGTCAAGATATCTGAACAGCAGGCAGAAAAAATTCTCAAGAG  
CATGGATAAAAAACGGCACGATGACCATCGACTGGAACGAGTGGAGAGACTACCACCTCCTCC  
ACCCCGTGGAACATCCCCGAGATCATCCTCTACTGGAAGCATTCCACGATCTTTGATGTG  
GGTGAGAATCTAACGGTCCCGGATGAGTTCACAGTGGAGGAGAGGCAGACGGGGATGTGGTG  
GAGACACCTGGTGGCAGGAGGTGGGGCAGGGGCCGTATCCAGAACCTGCACGGCCCCCTGG  
ACAGGCTCAAGGTGCTCATGCAGGTCCATGCCTCCCGCAGCAACAACATGGGCATCGTTGGT  
GGCTTCACTCAGATGATTCGAGAAGGAGGGGCCAGGTCACTCTGGCGGGGCAATGGCATCAA  
CGTCCTCAAAATTGCCCCCGAATCAGCCATCAAATTCATGGCCTATGAGCAGATCAAGCGCC  
TTGTTGGTAGTGACCAGGAGACTCTGAGGATTACAGAGAGGCTTGTGGCAGGGTCCTTGGCA  
GGGGCCATCGCCAGAGCAGCATCTACCCAATGGAGGTCTGAAGACCCGGATGGCGCTGCG  
GAAGACAGGCCAGTACTCAGGAATGCTGGACTGCGCCAGGAGGATCCTGGCCAGAGAGGGGG  
TGGCCGCTTCTACAAAGGCTATGTCCCAACATGCTGGGCATCATCCCCTATGCCGGCATC  
GACCTTGCAGTCTACGAGACGCTCAAGAATGCCTGGCTGCAGCACTATGCAGTGAACAGCGC  
GGACCCCGGCGTGTTTGTGCTCCTGGCCTGTGGCACCATGTCCAGTACCTGTGGCCAGCTGG  
CCAGCTACCCCTGGCCCTAGTCAGGACCCGGATGCAGGCGCAAGCCTCTATTGAGGGCGCT  
CCGGAGGTGACCATGAGCAGCCTCTTCAAACATATCCTGCGGACCGAGGGGGCCTTCGGGCT  
GTACAGGGGGCTGGCCCCCAACTTCATGAAGGTTCATCCAGCTGTGAGCATCAGCTACGTGG  
TCTACGAGAACCTGAAGATCACCTGGGCGTGCAGTCGCGGTGAAGGGGGGAGGGCCGCCCG  
GCAGTGGACTCGCTGATCCTGGGCCGCAGCCTGGGGTGTGCAGCCATCTCATTCTGTGAATG  
TGCCAACACTAAGCTGTCTCGAGCCAAGCTGTGAAAACCTAGACGCACCCGCAGGGAGGGT  
GGGGAGAGCTGGCAGGCCAGGGCTTGTCTGCTGACCCAGCAGACCCCTCCTGTTGGTTCC  
AGCGAAGACCACAGGCATTCCTTAGGGTCCAGGGTCAGCAGGCTCCGGGCTCACATGTGTAA  
GGACAGGACATTTTCTGCAGTGCCTGCCAATAGTGAGCTTGGAGCCTGGAGGCCGGCTTAGT  
TCTTCCATTTACCCCTTGCAGCCAGCTGTTGGCCACGGCCCCCTGCCCTCTGGTCTGCCGTGC  
ATCTCCCTGTGCCCTCTTGCTGCCTGCCTGTCTGCTGAGGTAAGGTGGGAGGAGGGCTACAG  
CCCACATCCCACCCCTCGTCCAATCCCATAATCCATGATGAAAGGTGAGGTACGTGGCCT  
CCCAGGCCTGACTTCCCAACCTACAGCATTGACGCCAAGCTTGGCTGTGAAGGAAGAGGAAAG  
GATCTGGCCTTGTGGTCACTGGCATCTGAGCCCTGCTGATGGCTGGGGCTCTCGGGCATGCT  
TGGGAGTGCAGGGGGCTCGGGCTGCCTGGCCTGGCTGCACAGAAGGCAAGTGCTGGGGCTCA  
TGGTGTCTGAGCTGGCCTGGACCCTGTGAGGATGGGCCCCACCTCAGAACCAAACTCACTG  
TCCCCACTGTGGCATGAGGGCAGTGGAGCACCATGTTTGAGGGCGAAGGGCAGAGCGTTTGT  
GTGTTCTGGGGAGGGAAGGAAAAGGTGTTGGAGGCCTTAATTATGGACTGTTGGGAAAAGGG  
TTTTGTCCAGAAGGACAAGCCGGACAAATGAGCGACTTCTGTGCTTCCAGAGGAAGACGAGG  
GAGCAGGAGCTTGGCTGACTGCTCAGAGTCTGTTCTGACGCCCTGGGGGTTCTGTCCAACC  
CCAGCAGGGGCGCAGCGGGACCAGCCCCACATTCACCTTGTGTCACTGCTTGGAACTATTT  
ATTTTGTATTTATTTGAACAGAGTTATGTCCTAACTATTTTTATAGATTTGTTTAATTAATA  
GCTTGTCAATTTCAAGTTCATTTTTTTATTCATATTTATGTTTCATGGTTGATTGTACCTTCCC  
AAGCCCGCCAGTGGGATGGGAGGAGGAGGAGAAGGGGGGCTTGGGCCGCTGCAGTCACAT  
CTGTCCAGAGAAATTCCTTTTGGGACTGGAGGCAGAAAAGCGGCCAGAAGGCAGCAGCCCTG  
GCTCCTTTCTTTGGCAGGTTGGGGAAAGGGCTTGCCCCCAGCCTTAGGATTTACAGGGTTTGA  
CTGGGGGCGTGGAGAGAGAGGGAGGAACCTCAATAACCTTGAAGGTGGAATCCAGTTATTTCT  
CTGCGCTGCGAGGGTTTCTTTATTTCACTCTTTTCTGAATGTCAAGGCAGTGAAGTGCCTCT  
CACTGTGAATTTGTGGTGGGCGGGGGCTGGAGGAGAGGGTGGGGGGCTGGCTCCGTCCCTCC  
CAGCCTTCTGCTGCCCTTGCTTAACAATGCCGGCCAAGTGGCGACCTCACGGTTGCACTTCC  
ATTCACACAGAATGACCTGATGAGGAAATCTTCAATAGGATGCAAGATCAATGCAAAAATT  
GTTATATATGAACATATAACTGGAGTCGTCAAAAAGCAAATTAAGAAAGAATTGGACGTTAG  
AAGTTGTCAATTTAAAGCAGCCTTCTAATAAAGTTGTTTCAAAGCTGAAAAAAGAAAAA  
AAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAAAGAAAAA

**FIGURE 206**

MLCLCLYVPVIGEAQTEFQYFESKGLPAELKSIFKLSVFIPSQEFSTYRQWKQKIVQAGDKD  
LDGQLDFEEFVHYLQDHEKKLRLVFKILDKKNDGRIDAQEIMQSLRDLGVKISEQQAEEKILK  
SMDKNGTMTIDWNEWRDYHLLHPVENIPEIILYWKHSTIFDVGENLTVPDEFTVEERQTGMW  
WRHLVAGGGAGAVSRTCTAPLDRLKVLMOVHASRSNNMGIVGGFTQMIREGGARSLWRGNGI  
NVLKIAPESAIKFMAYEQIKRLVGSDQETLRIHERLVAGSLAGAI AQSSIYPMEVLKTRMAL  
RKTGQYSGMLDCARRILAREGVAAFYKGYVPNMLGIIPYAGIDLAVYETLKNAWLQHYAVNS  
ADPGV FVLLACGTMSSTCGQLASYPLALVRTRMQAQASIEGAPEVTMSSLFKHILRTEGAFG  
LYRGLAPNFMKVIPAVSISYVVYENLKITLGVQSR

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**FIGURE 207**

GGAAGGCAGCGGCAGCTCCACTCAGCCAGTACCCAGATACGCTGGGAACCTTCCCCAGCCAT  
GGCTTCCCTGGGGCAGATCCTCTTCTGGAGCATAATTAGCATCATCATTATTCTGGCTGGAG  
CAATTGCACTCATCATTGGCTTTGGTATTTTCAGGGAGACACTCCATCACAGTCACTACTGTC  
GCCTCAGCTGGGAACATTGGGGAGGATGGAATCCTGAGCTGCACCTTTTGAACCTGACATCAA  
ACTTTCTGATATCGTGATAACAATGGCTGAAGGAAGGTGTTTTAGGCTTGGTCCATGAGTTCA  
AAGAAGGCAAAGATGAGCTGTCTGGAGCAGGATGAAATGTTCAGAGGCCGGACAGCAGTGTTT  
GCTGATCAAGTGATAGTTGGCAATGCCTCTTTGCGGCTGAAAAACGTGCAACTCACAGATGC  
TGGCACCTACAAATGTTATATCATCACTTCTAAAGGCAAGGGGAATGCTAACCTTGAGTATA  
AAACTGGAGCCTTCAGCATGCCGGAAGTGAATGTGGACTATAATGCCAGCTCAGAGACCTTG  
CGGTGTGAGGCTCCCCGATGGTTCCCCCAGCCCACAGTGGTCTGGGCATCCCAAGTTGACCA  
GGGAGCCAACTTCTCGGAAGTCTCCAATACCAGCTTTGAGCTGAACTCTGAGAATGTGACCA  
TGAAGGTTGTGTCTGTGCTCTACAATGTTACGATCAACAACACATACTCCTGTATGATTGAA  
AATGACATTGCCAAAGCAACAGGGGATATCAAAGTGACAGAATCGGAGATCAAAAGGCGGAG  
TCACCTACAGCTGCTAAACTCAAAGGCTTCTCTGTGTGTCTCTTCTTTCTTTGCCATCAGCT  
GGGCACTTCTGCCTCTCAGCCCTTACCTGATGCTAAAATAATGTGCCTTGGCCACAAAAAAG  
CATGCAAAGTCATTGTTACAACAGGGATCTACAGAACTATTTACCACCAGATATGACCTAG  
TTTTATATTTCTGGGAGGAAATGAATTCATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCA  
AGAAACAAAAAGAAGCCAAAAGCAGAAGGCTCCAATATGAACAAGATAAATCTATCTTCAAA  
GACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAAGAGTGATAAG  
TAAATGCACGTGGAGACAAGTGCATCCCCAGATCTCAGGGACCTCCCCCTGCCTGTCACCT  
GGGGAGTGAGAGGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTTTAGTTATATGTGCTG  
TAATGTTGCTCTGAGGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCA  
CAAATTAAGCTGTAGTATGTACCCTAAGACGCTGCTAATTGACTGCCACTTCGCAACTCAGG  
GGCGGCTGCATTTTGTAGTAATGGGTCAAATGATTCACCTTTTTATGATGCTTCCAAAGGTGCCT  
TGGCTTCTCTTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATAATTTTAGCATAA  
ACAGAGCAGTCGGGGACACCGATTTTATAAATAAACTGAGCACCTTCTTTTTAAACAAAAAA  
AA

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**FIGURE 208**

MASLGQILFWSIISIIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDI  
KLSDIVIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTD  
AGTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPOPTVWVASQVD  
QGANFSEVSNTSFELNSENVTMKVVSVLNVTINNTYSCMIENDIAKATGDIKVTESEIKRR  
SHLQLLNSKASLCVSSFFAISWALLPLSPYLMLK



[illegible]

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**FIGURE 210**

MAASLGQVLALVLVAALWGGTQPLLKRASAGLQRVHEPTWAQQLQEMKTLFLNTEYLM PFL  
LNQCGSLLYYLTLASTDLTLAVPICNSLAIIFTLIVGKALGEDIGGKRKLDYCECGTQLCGS  
RHTCVSSFPEPISP EWVRTRPFPILPFPLQLFCFLVAIRVPFPWTVWRKTEAGVWD

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**FIGURE 211**

CTTCTGTAGGACAGTCACCAGGCCAGATCCAGAAGCCTCTCTAGGCTCCAGCTTTCTCTGTG  
GAAGATGACAGCAATTATAGCAGGACCCTGCCAGGCTGTGCGAAAAGATTCCGCAATAAACT  
TTGCCAGTGGGAAGTACCTAGTGAAACGGCCTAAGATGCCACTTCTTCTCATGTCCCAGGCT  
TGAGGCCCTGTGGTCCCCATCCTTGGGAGAAGTCAGCTCCAGCACCAATGAAGGGCATCCTCG  
TTGCTGGTATCACTGCAGTGCTTGTTGCAGCTGTAGAATCTCTGAGCTGCGTGCAGTGTAAT  
TCATGGGAAAAATCCTGTGTCAACAGCATTGCCTCTGAATGTCCCTCACATGCCAACACCAG  
CTGTATCAGCTCCTCAGCCAGCTCCTCTCTAGAGACACCAGTCAGATTATAACCAGAATATGT  
TCTGCTCAGCGGAGAACTGCAGTGAGGAGACACACATTACAGCCTTCACTGTCCACGTGTCT  
GCTGAAGAACAACCTTTTCATTTTGTAAGCCAGTGCTGCCAAGGAAAGGAATGCAGCAACACCAG  
CGATGCCCTGGACCCTCCCCTGAAGAACGTGTCCAGCAACGCAGAGTGCCCTGCTTGTTATG  
AATCTAATGGAACCTTCCTGTCGTGGGAAGCCCTGGAAATGCTATGAAGAAGAACAGTGTGTC  
TTTCTAGTTGCAGAACTTAAGAATGACATTGAGTCTAAGAGTCTCGTGCTGAAAGGCTGTTC  
CAACGTCAGTAACGCCACCTGTCAGTTCCTGTCTGGTGAAAACAAGACTCTTGGAGGAGTCA  
TCTTTCGAAAGTTTGAGTGTGCAAATGTAAACAGCTTAACCCCCACGTCTGCACCAACCACT  
TCCCACAACGTGGGCTCCAAAGCTTCCCTCTACCTCTTGGCCCTTGCCAGCCTCCTTCTTCG  
GGGACTGCTGCCCTTGAGGTCTGGGGCTGCACTTTGCCCAGCACCCCATTCTGCTTCTCTG  
AGGTCCAGAGCACCCCCTGCGGTGCTGACACCCTCTTTCCCTGCTCTGCCCCGTTTAACTGC  
CCAGTAAGTGGGAGTCACAGGTCTCCAGGCAATGCCGACAGCTGCCTTGTTCTTCATTATTA  
AAGCACTGGTTCATTCACTGCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

**FIGURE 212**

MKGILVAGITAVLVAAVESLSCVQCNSWEKSCVNSIASECPSHANTSCISSSASSSLETPVR  
LYQNMFCSAENCSEETHITAFTVHVSAEEHFHFVSQCCQGKECSNTSDALDPPLKNVSSNAE  
CPACYESNGTSCRGKPWKCYEEEQCVFLVAELKNDIESKSLVLKGCSNVSNATCQFLSGENK  
TLGGVIFRKFEKANVNSLTPTSAPTTSNHNVGSKASLYLLALASLLLRGLLP



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**FIGURE 213**

GGCCTCGGTTCAAACGACCCGGTGGGTCTACAGCGGAAGGGAGGGAGCGAAGGTAGGAGGCA  
GGGCTTGCCTCACTGGCCACCCTCCCAACCCCAAGAGCCCAGCCCCATGGTCCCCGCCGCCG  
GCGCGCTGCTGTGGGTCTGCTGCTGAATCTGGGTCCCCGGGCGGCGGGGGCCCAAGGCCTG  
ACCCAGACTCCGACCGAAATGCAGCGGGTCAGTTTACGCTTTGGGGGGCCCCATGACCCGCAG  
CTACCGGAGCACC GCCCGGACTGGTCTTCCCCGGAAGACAAGGATAATCCTAGAGGACGAGA  
ATGATGCCATGGCCGACGCCGACCGCCTGGCTGGACCAGCGGCTGCCGAGCTCTTGGCCGCC  
ACGGTGTCCACCGGCTTTAGCCGGTCGTCCGCCATTAACGAGGAGGATGGGTCTTCAGAAGA  
GGGGGTGTGATTAATGCCGGAAGGATAGCACCAGCAGAGAGCTTCCCAGTGCGACTCCCA  
ATACAGCGGGGAGTTCCAGCACGAGGTTTATAGCCAATAGTCAGGAGCCTGAAATCAGGCTG  
ACTTCAAGCCTGCCGCGCTCCCCCGGGAGGTCTACTGAGGACCTGCCAGGCTCGCAGGCCAC  
CCTGAGCCAGTGGTCCACACCTGGGTCTACCCCGAGCCGGTGGCCGTCACCCTCACCCACAG  
CCATGCCATCTCCTGAGGATCTGCGGCTGGTGCTGATGCCCTGGGGGCCCGTGGCACTGCCAC  
TGCAAGTCGGGCACCATGAGCCGGAGCCGGTCTGGGAAGCTGCACGGCCTTTCCGGGCGCCT  
TCGAGTTGGGGCGCTGAGCCAGCTCCGCACGGAGCACAAGCCTTGACACCTATCAACAATGTC  
CCTGCAACCGACTTCGGGAAGAGTGCCCCCTGGACACAAGTCTCTGTACTGACACCAACTGT  
GCCTCTCAGAGCACCACCAGTACCAGGACCACCACTACCCCCTTCCCCACCATCCACCTCAG  
AAGCAGTCCCAGCCTGCCACCCGCCAGCCCCTGCCAGCCCTGGCTTTTTTGGAACGGGTCA  
GGATTGGCCTGGAGGATATTTGGAATAGCCTCTCTTCAGTGTTACAGAGATGCAACCAATA  
GACAGAAACCAGAGGTAATGGCCACTTCATCCACATGAGGAGATGTCAGTATCTCAACCTCT  
CTTGCCCTTTCAATCCTAGCACCCACTAGATATTTTTAGTACAGAAAAACAAAACCTGGAAAA  
CACAA

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**FIGURE 214**

MVPAAGALLWVLLLNLGPRAAGAQGLTQTPTEMQRVSLRFGGPMTRSYRSTARTGLPRKTRI  
ILEDENDAMADADRLAGPAAAELLAATVSTGFSSAINEDGSSEEGVVINAGKDSTSREL  
PSATPNTAGSSSTRFIANSQEPEIRLTSSLPRSPGRSTEDLPGSQATLSQWSTPGSTPSRWP  
SPSPTAMPSPEDLRLVLMPWGPWHCHCKSGTMSRSRSGKLHGLSGRLRVGALSQLRTEHKPC  
TYQQCPCNRLREECPLDTSLCDTNCASQSTTSTRTTTTTFPTIHLRSSPSLPPASPCPALA  
FWKRVRIGLEDIWNSLSSVFTEMQPIDRNQR

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**FIGURE 215**

CCCGGGTCGACCCACGCGTCCGGGGAGAAAGGATGGCCGGCCTGGCGGCGCGGTGGTCTCTG  
CTAGCTGGGGCAGCGGCGCTGGCGAGCGGCTCCCAGGGCGACCGTGAGCCGGTGTACCGCGA  
CTGCGTACTGCAGTGCGAAGAGCAGAACTGCTCTGGGGGCGCTCTGAATCACTTCCGCTCCC  
GCCAGCCAATCTACATGAGTCTAGCAGGCTGGACCTGTCGGGACGACTGTAAGTATGAGTGT  
ATGTGGGTCAACGTTGGGCTCTACCTCCAGGAAGGTCAAAAGTGCCTCAGTTCCATGGCAA  
GTGGCCCTTCTCCCGGTTCTGTTCTTTCAAGAGCCGGCATCGGCCGTGGCCTCGTTTCTCA  
ATGGCCTGGCCAGCCTGGTGATGCTCTGCCGCTACCGCACCTTCGTGCCAGCCTCCTCCCCC  
ATGTACCACACCTGTGTGGCCTTCGCCTGGGTGTCCCTCAATGCATGGTTCTGGTCCACAGT  
CTTCCACACCAGGGACACTGACCTCACAGAGAAAATGGACTACTTCTGTGCCTCCACTGTCA  
TCCTA CACTCAATCTACCTGTGCTGCGTCAGGACCGTGGGGCTGCAGCACCCAGCTGTGGTC  
AGTGCCTTCCGGGCTCTCCTGCTGCTCATGCTGACCGTGCACGTCTCCTACCTGAGCCTCAT  
CCGCTTCGACTATGGCTACAACCTGGTGGCCAACGTGGCTATTGGCCTGGTCAACGTGGTGT  
GGTGGCTGGCCTGGTGCCTGTGGAACCAGCGGCGGCTGCCTCACGTGCGCAAGTGCGTGGTG  
GTGGTCTTGCTGCTGCAGGGGCTGTCCCTGCTCGAGCTGCTTGACTTCCCACCGCTCTTCTG  
GGTCCTGGATGCCCATGCCATCTGGCACATCAGCACCATCCCTGTCCACGTCCTCTTTTTCA  
GCTTTCTGGAAGATGACAGCCTGTACCTGCTGAAGGAATCAGAGGACAAGTTCAAGCTGGAC  
TGAAGACCTTGGAGCGAGTCTGCCCCAGTGGGGATCCTGCCCCCGCCCTGCTGGCCTCCCTT  
CTCCCCTCAACCCTTGAGATGATTTTCTCTTTTCAACTTCTTGAACCTTGGACATGAAGGATG  
TGGGCCCAGAATCATGTGGCCAGCCCACCCCCTGTTGGCCCTCACCAGCCTTGGAGTCTGTT  
CTAGGGAAGGCCTCCCAGCATCTGGGACTCGAGAGTGGGCAGCCCCTCTACCTCCTGGAGCT  
GAACTGGGGTGGAAGTGAAGTGTGTTCTTAGCTCTACCGGGAGGACAGCTGCCTGTTTCCTCC  
CCACCAGCCTCCTCCCCACATCCCCAGCTGCCTGGCTGGGTCTGAAGCCCTCTGTCTACCT  
GGGAGACCAGGGACCACAGGCCTTAGGGATACAGGGGGTCCCCCTTCTGTTACCAACCCCCAC  
CCTCCTCCAGGACACGACTAGGTGGTGCTGGATGCTTGTTCTTTGGCCAGCCAAGGTTACAG  
GCGATTCTCCCCATGGGATCTTGAGGGACCAAGCTGCTGGGATTGGGAAGGAGTTTCACCT  
GACCGTTGCCCTAGCCAGGTTCCCAGGAGGCCTCACCATACTCCCTTTCAGGGCCAGGGCTC  
CAGCAAGCCCAGGGCAAGGATCCTGTGCTGCTGTCTGGTTGAGAGCCTGCCACCGTGTGTG  
GGAGTGTGGGCCAGGCTGAGTGCATAGGTGACAGGGCCGTGAGCATGGGCCTGGGTGTGTGT  
GAGCTCAGGCCTAGGTGCGCAGTGTGGAGACGGGTGTTGTGCGGGAAGAGGTGTGGCTTCAA  
AGTGTGTGTGTGCAGGGGGTGGGTGTGTTAGCGTGGGTAGGGGAACGTGTGTGCGCGTGCT  
GGTGGGCATGTGAGATGAGTGAAGTGAATGTGTCCACAGTTGAGAGGTTGGAGCAGG  
ATGAGGGAATCCTGTCACCATCAATAATCACTTGTGGAGCGCCAGCTCTGCCCAAGACGCCA  
CCTGGGCGGACAGCCAGGAGCTCTCCATGGCCAGGCTGCCTGTGTGCATGTTCCCTGTCTGG  
TGCCCCCTTTGCCCGCCTCCTGCAAACCTCACAGGGTCCCCACACAACAGTGCCCTCCAGAAG  
CAGCCCCCTCGGAGGCAGAGGAAGGAAAATGGGGATGGCTGGGGCTCTCTCCATCCTCCTTTT  
CTCCTTGCCCTTCGCATGGCTGGCCTTCCCCCTCCAAAACCTCCATTCCCCTGCTGCCAGCCCC  
TTTGCCATAGCCTGATTTTGGGGAGGAGGAAGGGGCGATTTGAGGGAGAAGGGGAGAAAGCT  
TATGGCTGGGTCTGGTTTCTTCCCTTCCCAGAGGGTCTTACTGTTCCAGGGTGGCCCCAGGG  
CAGGCAGGGGCCACACTATGCCTGTGCCCTGGTAAAGGTGACCCCTGCCATTTACCAGCAGC  
CCTGGCATGTTCTGCCCCACAGGAATAGAATGGAGGGAGCTCCAGAACTTTCCATCCCAA  
AGGCAGTCTCCGTGGTTGAAGCAGACTGGATTTTGTCTGCCCCCTGACCCCTTGTCCCTCT  
TTGAGGGAGGGGAGCTATGCTAGGACTCCAACCTCAGGGACTCGGGTGGCCTGCGCTAGCTT  
CTTTTGATACTGAAAACCTTTTAAGGTGGGAGGGTGGCAAGGGATGTGCTTAATAAATCAATT  
CCAAGCCTCAAAAAAAAAAAAAAAAAA

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**FIGURE 216**

MAGLAARLVLLAGAAALASGSQGDREPVYRDCVLQCEEQNCSGGALNHFRSRQPIYMSLAGW  
TCRDDCKYECMWVTVGLYLQEGHKVPQFHGKWPF SRFLFFQEPASAVASFLNGLASLVMLCR  
YRTFVPASSPMYHTCVAFAWVSLNAWFWSTVFHTRDTDLTEKMDYFCASTVILHSIYLCCVR  
TVGLQHPAVVSAFRALLLLMLTVHVSYSLSLIRFDYGYNLVANVAIGLVNVVWWLAWCLWNQR  
RLPHVRKCVVVVLLLQGLSLLELLDFPPLFWVLDAAHAIWHISTIPVHVLFFSFLEDDSLYLL  
KESEDKFKLD



## FIGURE 217

[illegible]

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**FIGURE 218**

MAPQSLPSSRMAPLGMLLGLLMAACFTFCLSHQNLKEFALTNPESSTKETERKETKAEEL  
DAEVLEVFHPTHEWQALQPGQAVPAGSHVRLNLQTGEREAKLQYEDKFRNNLKGKRLDINTN  
TYTSQDLKSALAKFKEGAEMESSKEDKARQAEVKRLFRPIEELKKDFDELNVVIETDMQIMV  
RLINKFNSSSSSLEEKIAALFDLEYVHQMDNAQDLLSFGGLQVVINGLNSTEPLVKEYAAF  
VLGAAFSSNPKVQVEAIEGGALQKLLVILATEQPLTAKKKVLFALCSLLRHFPYAQRQFLKL  
GGLQVLRRTLQVEKGTEVLAVRVVTLLYDLVTEKMFEEEEAELTQEMSPEKLQQYRQVHLLPG  
LWEQGWCEITAHLLALPEHDAREKVLQTLGVLLTTCRDRYRQDPQLGRTLASLQAEYQVLAS  
LELQDGEDEGYFQELLGSVNSLLKELR

## FIGURE 219

TTCGGCTTCCGTAGAGGAAGTGGCGCGGACCTTCATTTGGGGTTCGGGTTCCTCCCCCTTCCC  
CTTCCCCGGGGTCTGGGGGTGACATTGCACCGCGCCCCCTCGTGGGGTCGCGTTGCCACCCCA  
CGCGGACTCCCCAGCTGGCGCGCCCCCTCCCATTTGCCTGTCTGGTCAGGCCCCACCCCCC  
TTCCCACCTGACCAGCCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTGCGGTTCGGC  
CCGGCCTTCGCGCTTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGT  
CGCAGGGGCATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGG  
TCCATGTGACCGACCGGTGAGATGCCCGGCTCCAGTACGGCCTCCTGATTTTTTGGTGCTGCT  
GTCTCTGTCCTTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGA  
TGAAGGGTTAGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCT  
ATGTTTTCTGGTCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTTGGCT  
GATGCACTTGGGCCAGGTGTGGTTGGGATCCATGGAGACTCACCTATTACTTCCTGACTTC  
AGCCTTTCTGACAGCAGCCATTATCCTGCTCCATACCTTTTGGGGAGTTGTGTTCTTTGATG  
CCTGTGAGAGGAGACGGTACTGGGCTTTGGGCCTGGTGGTTGGGAGTCACCTACTGACATCG  
GGACTGACATTCTGAACCCCTGGTATGAGGCCAGCCTGCTGCCCATCTATGCAGTCACTGT  
TTCCATGGGGCTCTGGGCCTTCATCACAGCTGGAGGGTCCCTCCGAAGTATTCAGCGCAGCC  
TCTTGTGTAAGGACTTGACTACCTGGACTGATCGCCTGACAGATCCCACCTGCCTGTCCACTG  
CCCATGACTGAGCCCAGCCCCAGCCCCGGGTCCATTGCCACATTCTCTGTCTCCTTCTCGTC  
GGTCTACCCCACCTACCTCCAGGGTTTTGCTTTGTCTTTTTGTGACCGTTAGTCTCTAAGCTT  
TACCAGGAGCAGCCTGGGTTCAGCCAGTCAGTGACTGGTGGGTTTGAATCTGCACTTATCCC  
CACCACCTGGGGACCCCCCTTGTTGTGTCCAGGACTCCCCCTGTGTCAGTGCTCTGCTCTCAC  
CCTGCCCAAGACTCACCTCCCTTCCCCCTCTGCAGGCCGACGGCAGGAGGACAGTCGGGTGAT  
GGTGTATTCTGCCCTGCGCATCCCACCCGAGGACTGAGGGAACCTAGGGGGGACCCCTGGGC  
CTGGGGTGCCCTCCTGATGTCCTCGCCCTGTATTTCTCCATCTCCAGTTCTGGACAGTGACAG  
GTTGCCAAGAAAAGGGACCTAGTTTAGCCATTGCCCTGGAGATGAAATTAATGGAGGCTCAA  
GGATAGATGAGCTCTGAGTTTCTCAGTACTCCCTCAAGACTGGACATCTTGGTCTTTTTTCTC  
AGGCCTGAGGGGGAACCATTTTTTGGTGTGATAAAATACCCTAAACTGCCTTTTTTTTTCTTTTTT  
GAGGTGGGGGGAGGGAGGAGGTATATTGGAACCTCTTCTAACCTCCTTGGGCTATATTTTCTC  
TCCTCGAGTTGCTCCTCATGGCTGGGCTCATTTTCGGTCCCTTTCTCCTTGGTCCCAGACCTT  
GGGGGAAAGGAAGGAAGTGATGTTTGGGAACTGGCATTACTGGAACATAATGGTTTTTAACCT  
CCTTAACCACCAGCATCCCTCCTCTCCCCAAGGTGAAGTGGAGGGTGCTGTGGTGAGCTGGC  
CACTCCAGAGCTGCAGTGCCACTGGAGGAGTCAGACTACCATGACATCGTAGGGAAGGAGGG  
GAGATTTTTTTGTAGTTTTTAATTGGGGTGTGGGAGGGGCGGGGAGGTTTTTCTATAAACTGT  
ATCATTTTTCTGCTGAGGGTGGAGTGTCCCATCCTTTTAATCAAGGTGATTGTGATTTTTGACT  
AATAAAAAAGAATTTGTAAAAA  
AAAAA

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**FIGURE 220**

MGA AVFFGCTFVAFGPAFALFLITVAGDPLRVII LVAGAFFWLVSLLLASVVWFILVHVTDR  
SDARLQYGLLIFGA AVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYVSGLS  
FGIISGVFSVINILADALGPGVVG I HG DSPYYFLTSAFLTA AIILLHTFWGVVFFDACERRR  
YWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQRSLLCKD



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**FIGURE 221**

AAGCTGGTTTAAGGAAGCAGAGGAGGGTTAGATTCGTTGAGTGAGGACGGAAGATCAACCCA  
TTTCCATTCCGCCAGATGGCCTATGTTTCTGGTCTCTCCCTTCGGNATCATCAGTGGTGTNT  
TNTCTGTTATCAATATTTTGGCTGATGCANTTGGGCCAGGTGTGGTTGGGATCCATGGAGAC  
TCACCCTATTANTTCCTGANTTCAGCCTTTNTGACAGCAGCCATTATCCTGCTC

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**FIGURE 222**

GACCGACCGTTCAGATGCCCCGGTTCAGTACGGCTTCCTGATTTTTGGTGCTGCTGTNTCTG  
TCCTTCTACAGGAGGTGTTCCGCTTTGCCTANTACAAGCTGCTTAAGAAGGCAGATGAGGGG  
TTAGCATNGCTGAGTGAGGACGGAAGATCACCCATTTCCATCCGCCAGATGGCCTATGTTTN  
TGGTNTTTCCTTCGGTATCATCAGTGGTGTTTTNTCTGTTATCAATATTTTGGNTGATGCAN  
TTGGGCCAGGTGTGGTTGGGATCCATGGAGANTCACCTATTAATTCCTGAATTCAGCCTTT  
NTGACAGCAGCCATTATCCTGNTCCATACCTTTTGGGGAGTTGTGTTTTTTGATGCCTGTGA  
GAGGAG

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**FIGURE 223**

NGTTGGAGAAGTGGCGCGGACNTTCATTTGGGGTTTCGGTTTCCCCCCTTTCCCTTTCCCCG  
GGGTCTGGGGTGACATTGCACGGGGCCCCTCGTGGGGTCGCGTTGCCACCCACGCGGACTCC  
CCAGNTGGNGCGCCCTTCCCATTTCCTGTCTGGTCAGGCCCCCACCCTTCCCACNTG  
ACCAGCCATGGGGGCTGCGGTGTTTTTCGGCTGCACTTTCGTGCGGTTCCGGCCCGGCCTTCG  
CGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTCGCAGGGGCA  
TTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGGTCCATGTGAC  
CGACCGGTCAGATGCCCCGGCTCCAGTACGGCCTCCTGATTTTTTGGTGCTGCTGTCTCTGTCC  
TTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGATGAGGGGTTA  
GCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTGG  
TCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTTG  
GGCCAGGTGTGGTTGGGATCCATGGAGACTCACCC

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**FIGURE 224**

GTAAAAGAAAGTGGCCGGACCTTCATTGGGGTTTCGGTTCCTCCCTTTCCCNNTTCCCCGGGG  
TCTGGGGGTGACATTGCACCGCGCCCNCTCGTGGGGTTCGCGTTGCCACCCACGCGGACTCCC  
CAGNTGGCGCGCCCTCCCATTTGCCTGTCCTGGTCAGGCCCCACCCCTTCCCACCTGA  
CCAGCCATGGGGGCTGCGGTGTTTTTCGGGCTGCACTTTCGTTCGCGTTTCGGGCCCGGCCTTC  
GCGCTTTTCTTGATCACTGTGGCTGGGGACCCGCTTCGCGTTATCATCCTGGTCGCAGGGGC  
ATTTTTCTGGCTGGTCTCCCTGCTCCTGGCCTCTGTGGTCTGGTTCATCTTGGTCCATGTGA  
CCGACCGGTCAGATGCCCCGGCTCCAGTACGGCCTCCTGATTTTTGGTGCTGCTGTCTCTGTC  
CTTCTACAGGAGGTGTTCCGCTTTGCCTACTACAAGCTGCTTAAGAAGGCAGATGAGGGGT  
AGCATCGCTGAGTGAGGACGGAAGATCACCCATCTCCATCCGCCAGATGGCCTATGTTTCTG  
GTCTCTCCTTCGGTATCATCAGTGGTGTCTTCTCTGTTATCAATATTTTGGCTGATGCACTT  
GGGCCAGGTGTGGTTGGGATCCATGGAGAC



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**FIGURE 225**

GCCCCAGGGAGCAGTGGGTGGTTATAACTCAGGCCCGGTGCCCAGAGCCCAGGAGGAGGCAG  
TGGCCAGGAAGGCACAGGCCTGAGAAGTCTGCGGCTGAGCTGGGAGCAAATCCCCACCCCC  
TACCTGGGGGACAGGGCAAGTGAGACCTGGTGAGGGTGGCTCAGCAGGCAGGGAAGGAGAGG  
TGTCTGTGCGTCCTGCACCCACATCTTTCTCTGTCCCCTCCTTGCCCTGTCTGGAGGCTGCT  
AGACTCCTATCTTCTGAATTCTATAGTGCCTGGGTCTCAGCGCAGTGCCGATGGTGGCCCGT  
CCTTGTGGTTCCTCTCTACCTGGGGAAATAAGGTGCAGCGGCCATGGCTACAGCAAGACCCC  
CCTGGATGTGGGTGCTCTGTGCTCTGATCACAGCCTTGCTTCTGGGGGTACAGAGCATGTT  
CTCGCCAACAATGATGTTTCCTGTGACCACCCCTCTAACACCGTGCCCTCTGGGAGCAACCA  
GGACCTGGGAGCTGGGGCCGGGGAAGACGCCCGGTGCGGATGACAGCAGCAGCCGCATCATCA  
ATGGATCCGACTGCGATATGCACACCAGCCGTGGCAGGCCGCGCTGTTGCTAAGGCCCAAC  
CAGCTCTACTGCGGGGCGGTGTTGGTGCATCCACAGTGGCTGCTCACGGCCGCCCACTGCAG  
GAAGAAAGTTTTTCAGAGTCCGTCTCGGCCACTACTCCCTGTCACCAGTTTATGAATCTGGGC  
AGCAGATGTTCCAGGGGGTCAAATCCATCCCCACCCTGGCTACTCCCACCCTGGCCACTCT  
AACGACCTCATGCTCATCAAACCTGAACAGAAGAATTCGTCCCACTAAAGATGTCAGACCCAT  
CAACGTCTCCTCTCATTGTCCCTCTGCTGGGACAAAGTGCTTGGTGTCTGGCTGGGGGACAA  
CCAAGAGCCCCCAAGTGCACTTCCCTAAGGTCCTCCAGTGCTTGAATATCAGCGTGCTAAGT  
CAGAAAAGGTGCGAGGATGCTTACCCGAGACAGATAGATGACACCATGTTCTGCGCCGGTGA  
CAAAGCAGGTAGAGACTCCTGCCAGGGTGATTCTGGGGGGCCTGTGGTCTGCAATGGCTCCC  
TGCAGGGACTCGTGTCTTGGGGAGATTACCCTTGTGCCCGGCCCAACAGACCGGGTGTCTAC  
ACGAACCTCTGCAAGTTCACCAAGTGGATCCAGGAAACCATCCAGGCCAACTCCTGAGTCAT  
CCCAGGACTCAGCACACCGGCATCCCCACCTGCTGCAGGGACAGCCCTGACACTCCTTTCAG  
ACCCTCATTCCTTCCCAGAGATGTTGAGAATGTTTCATCTCTCCAGCCCCTGACCCCATGTCT  
CCTGGACTCAGGGTCTGCTTCCCCCACATTGGGCTGACCGTGTCTCTCTAGTTGAACCCTGG  
GAACAATTTCCAAAACCTGTCCAGGGCGGGGGTTCGTCTCAATCTCCCTGGGGCACTTTCAT  
CCTCAAGCTCAGGGCCCATCCCTTCTCTGCAGCTCTGACCCAAATTTAGTCCCAGAAATAAA  
CTGAGAAGTGGAAAAA

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**FIGURE 226**

MATARPPWMVLCALITALLGVTEHVLANNVSCDHPSNTVPSGSNQDLGAGAGEDARSDD  
SSSRIINGSDCDMHTQPWQAALLLRPNQLYCGAVLVHPQWLLTAAHCRKKVFRVRLGHYSLS  
PVYESGQQMFQGVKSIHPHGYSHPGHSNDLMLIKLNRRIRPTKDVRPINVSSHCP SAGTKCL  
VSGWGTTKSPQVHF PKVLQCLNISVLSQKRCEDAYPRQIDDTMFCAGDKAGR DSCQGD SGGP  
VVCNGSLQGLVSWGDYPCARPNRPGVYTNLCKFTKWIQETIQANS

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**FIGURE 227**

ATGGTCAACGACCGGTGGAAGACCATGGGCGGCGCTGCCCAACTTGAGGACCGGCCGCGCGA  
CAAGCCGCAGCGGCCGAGCTGCGGCTACGTGCTGTGCACCGTGCTGCTGGCCCTGGCTGTGC  
TGCTGGCTGTAGCTGTACCCGGTGCCGTGCTCTTCCTGAACACGCCACGCGCCGGGCACG  
GCGCCCCCACCTGTCGTCAGCACTGGGGCTGCCAGCGCCAAACAGCGCCCTGGTCACTGTGGA  
AAGGGCGGACAGCTCGCACCTCAGCATCCTCATTGACCCGCGCTGCCCCGACCTCACCGACA  
GCTTCGCACGCCTGGAGAGCGCCCAGGCCTCGGTGCTGCAGGCGCTGACAGAGCACCAGGCC  
CAGCCACGGCTGGTGGGCGACCAGGAGCAGGAGCTGCTGGACACGCTGGCCGACCAGCTGCC  
CCGGCTGCTGGCCCGAGCCTCAGAGCTGCAGACGGAGTGCATGGGGCTGCGGAAGGGGCATG  
GCACGCTGGGCCAGGGCCTCAGCGCCCTGCAGAGTGAGCAGGGCCGCTCATCCAGCTTCTC  
TCTGAGAGCCAGGGCCACATGGCTCACCTGGTGAACCTCCGTACGCGACATCCTGGATGCCCT  
GCAGAGGGACCGGGGGCTGGGCGGGCCCCGCAACAAGGCCGACCTTCAGAGAGCGCCTGCCC  
GGGGAACCCGGCCCCGGGGCTGTGCCACTGGCTCCCGGGCCCCGAGACTGTCTGGACGTCCTC  
CTAAGCGGACAGCAGGACGATGGCGTCTACTCTGTCTTTCCCACTTACCCGGCCGGCTT  
CCAGGTGTACTGTGACATGCGCACGGACGGCGGGCTGGACGGTGTTCAGCGCCGGGAGG  
ACGGCTCCGTGAACTTCTTCCGGGGCTGGGACGCGTACCGAGACGGCTTTGGCAGGCTCACC  
GGGGAGCACTGGCTAGGGCTCAAGAGGATCCACGCCCTGACCACACAGGCTGCCTACGAGCT  
GCACGTGGACCTGGAGGACTTTGAGAATGGCACGGCCTATGCCCGCTACGGGAGCTTCGGCG  
TGGGCTTGTCTCCGTGGACCCTGAGGAAGACGGGTACCCGCTCACCGTGGCTGACTATTCC  
GGCACTGCAGGCGACTCCCTCCTGAAGCACAGCGGCATGAGGTTCAACCACCAAGGACCGTGA  
CAGCGACCATTCAGAGAACAACCTGTGCCGCCTTCTACCGCGGTGCCTGGTGGTACCGCAACT  
GCCACACGTCCAACCTCAATGGGCGAGTACCTGCGCGGTGCGCACGCCTCCTATGCCGACGGC  
GTGGAGTGGTCTCCTGGACC GGCTGGCAGTACTCACTCAAGTTCTCTGAGATGAAGATCCG  
GCCGGTCCGGGAGGACCGCTAGACTGGTGCACCTTGTCTTGGCCCTGCTGGTCCCTGTGCG  
CCCATCCCCGACCCACCTCACTCTTTCGTGAATGTTCTCCACCCACCTGTGCCTGGCGGAC  
CCACTCTCCAGTAGGGAGGGGCGGGCCATCCCTGACACGAAGCTCCCTGGGCGCGTGAAGT  
CACACATCGCCTTCTCGCCGTCCCCACCCCTCCATTTGGCAGCTCACTGATCTCTTGCCCTC  
TGCTGATGGGGGCTGGCAAACCTTGACGACCCCAACTCCTGCCTGCCCCCACTGTGACTCCGG  
TGCTGTTTGCCGTCCCTGGCCAGGATGGTGGAGTCTGCCCCAGGCACCCTCTGCCCTGCCC  
GGCCAAATACCCGGCATTATGGGGACAGAGAGCAGGGGGCAGACAGCACCCTGGAGTCCTC  
CTAGCAGATCGTGGGGAATGTCAGGTCTCTCTGAGGTCAGGTCTGAGGCCAGTATCCTCCAG  
CCCTCCCAATGCCAACCCCCACCCCGTTTCCCTGGTGCCCAGAGAACCACCTCTCCCCCAA  
GGGCCTCAGCCTGGCTGTGGGCTGGGTGGCCCCATCCTACCAGGCCCTGAGGTCAGGATGGG  
GAGCTGCTGCCTTTGGGGACCCACGCTCCAAGGCTGAGACCAGTTCCCTGGAGGCCACCCAC  
CCTGTGCCCCGGCAGGCCTGGGGTCTGCAGTCTCTTACCTGCTGTGCCACCTGCTCTCTG  
TCTCAAATGAGGCCCAACCCATCCCCACCCAGCTCCCGGCCGTCTCCTACCTGGGGCAGC  
CGGGGCTGCCATCCCATTTCTCCTGCCTCTGGAAGGTGGGTGGGGCCCTGCACCGTGGGGCT  
GGACTGCGCTAATGGGAAGCTCTTGGTTTTCTGGGCTGGGGCCTAGGCAGGGCTGGGATGAG  
GCTTGTACAACCCCCACCACAATTTCCAGGGACTCCAGGGTCTGAGGCCCTCCAGGAGG  
GCCTTGGGGGTGATGACCCCTTCCCTGAGGTGGCTGTCTCCATGAGGAGGCCAACCCTTGCC  
ATTGACCGTGGCCACCTGGACCCAGGCCAGGCCCGGCCCGGCGAGTGGTCAAGGGACAGGGA  
CCACCTCACCGGGCAAATGGGGTGGGGGGGACTGGGGCACCAGACCAGGCACCACCTGGACA  
CTTTCTTGTGAATCCTCCCAACACCCAGCACGCTGTATCCCCACTCCTTGTGTGCACACA  
TGCAGAGGTGAGACCCGAGGCTCCAGGACCAGCAGCCACAAGGGCAGGGCTGGAGCCGGG  
TCCTCAGCTGTCTGCTCAGCAGCCCTGGACCCGCGTGCGTTACGTACGGCCAGATGCAGGG  
CGGCTTTTCCAAGGCCTCCTGATGGGGGCTCCGAAAGGGCTGGAGTCAGCCTTGGGGAGCT  
GCCTAGCAGCCTCTCCTCGGGCAGGAGGGGAGGTGGCTTCCTCCAAGGACACCCGATGGCA  
GGTGCCTAGGGGGTGTGGGGTTCCGTTCTCCCTTCCCTCCCACTGAAGTTTGTGCTTAAAA  
ACAATAAATTTGACTTGGCACCACTGGGGGTGGTGGGAGAGGCCGTGTGACCTGGCTCTC  
TGTCCAGTGCCACCAGGTCATCCACATGCGCAG

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**FIGURE 228**

MVNDRWKTMGGAAQLEDPRDPKQRPSCGYVLCTVLLALAVLLAVAVTGAVLFLNHAHAPGT  
APPPVVSTGAASANSALVTVERADSSHLNILIDPRCPDLTDSFARLESAQASVLQALTEHQA  
QPRLVGDQEQELDLADQLPRLARASELQTECMGLRKGHGTLGQGLSALQSEQGRLIQLL  
SESQGHMAHLVNSVSDILDALQDRGLGRPRNKADLQAPARGTRPRGCATGSRPRDCLDVL  
LSGQQDDGVYSVFPTHYPAGFQVYCDMRTDGGGWTVFQRRDGSVNFFRGWDAYRDGFGRLT  
GEHWLGLKRIHALTTQAAYELHVDLEDFENGTAARYGSFGVGLFSVDPEEDGYPLTVADYS  
GTAGDSLLKHSGMRFTTKDRDSDHSENNCAAFYRGAWWYRNCHTSNLNGQYLARGAHASYADG  
VEWSSWTGWQYSLKFSEMKIRPVREDR



**FIGURE 229**

GCAGTCAGAGACTTCCCCTGCCCCTCGCTGGGAAAGAACATTAGGAATGCCTTTTAGTGCCT  
TGCTTCCTGAACTAGCTCACAGTAGCCCGGCGGCCAGGGCAATCCGACCACATTTCACTCT  
CACCGCTGTAGGAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGCTGGATGATG  
ATGGGGACACCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACCTCGGCATCCAGAGCCC  
CGGCGCACAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGACCCTGCTGAC  
TTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTTCAGTACTACC  
AGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGATTAGGAAATACGTCC  
CAAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTCTGCAGCATGTGGC  
TGAAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGCACACAGGTGCAGCCCTTGTACAG  
AACAAATGGAAATGGCATGGAGACAATTGCTACCAGTTCTATAAAGACAGCAAAAGTTGGGAG  
GACTGTAAATATTTCTGCCTTAGTGAAAACTCTACCATGCTGAAGATAAACAAACAAGAAGA  
CCTGGAATTTGCCGCGTCTCAGAGCTACTCTGAGTTTTTCTACTCTTATTGGACAGGGCTTT  
TGCGCCCTGACAGTGGCAAGGCCTGGCTGTGGATGGATGGAACCCCTTTCACTTCTGAACTG  
TTCCATATTATAATAGATGTCACCAGCCCAAGAAGCAGAGACTGTGTGGCCATCCTCAATGG  
GATGATCTTCTCAAAGGACTGCAAAGAATTGAAGCGTTGTGTCTGTGAGAGAAGGGCAGGAA  
TGGTGAAGCCAGAGAGCCTCCATGTCCCCCTGAAACATTAGGCGAAGGTGACTTGATTCGCC  
CTCTGCAACTACAAATAGCAGAGTGAGCCAGGCGGTGCCAAAGCAAGGGCTAGTTGAGACAT  
TGGGAAATGGAACATAATCAGGAAAGACTATCTCTCTGACTAGTACAAAATGGGTTCTCGTG  
TTTCCTGTTTCAGGATCACCAGCATTTCTGAGCTTGGGTTTATGCACGTATTTAACAGTCACA  
AGAAGTCTTATTTACATGCCACCAACCAACCTCAGAAACCCATAATGTCATCTGCCTTCTTG  
GCTTAGAGATAACTTTTAGCTCTCTTTCTTCTCAATGTCTAATATCACCTCCCTGTTTTCAT  
GTCTTCCTTACACTTGGTGGAAATAAGAACTTTTTGAAGTAGAGGAAATACATTGAGGTAAC  
ATCCTTTTCTCTGACAGTCAAGTAGTCCATCAGAAATTGGCAGTCACTTCCCAGATTGTACC  
AGCAAATACACAAGGAATTCTTTTTGTTTGTTTCAGTTCATACTAGTCCCTTCCCAATCCAT  
CAGTAAAGACCCCATCTGCCTTGTCCATGCCGTTTCCCAACAGGGATGTCACCTTGATATGAG  
AATCTCAAATCTCAATGCCTTATAAGCATTCTTCTGTGTCCATTAAAGACTCTGATAATTG  
TCTCCCCTCCATAGGAATTTCTCCAGGAAAGAAATATATCCCCATCTCCGTTTCATATCAG  
AACTACCGTCCCCGATATTCCCTTCAGAGAGATTAAAGACCAGAAAAAAGTGAGCCTCTTCA  
TCTGCACCTGTAATAGTTTCAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTCAG  
GTACTGAAGATTTAATAATAATAAATGTAAATACTGTGAAAAA

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**FIGURE 230**

MQAKYSSTRDMLDDDGD TTMSLHSQASATTRHPEPRRTEHRAPSSTWRPVALTLLTLCLVLL  
IGLAALGLLFFQYYQLSNTGQDTISQMEERLGNTSQELQSLQVQNIKLAGSLQHVAEKLCRE  
LYNKAGAHRCSPCTEQWKWHGDNCYQFYKDSKSWEDCKYFCLSENSTMLKINKQEDLEFAAS  
QSYSEFFYSYWTGLLRPDSGKAWLWMDGTPFTSELFHIIIDVTSPRSRDCVAILNGMIFSKD  
CKELKRCVCERRAGMVKPESLHVPPETLGED

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**FIGURE 231**

AATTTTCACCGCTGTAGGAATCCAGATGCAGGCCAAGTACAGCAGCACGAGGGACATGNTGG  
ATGATGATGGGACACCACCATGAGCCTGCATTNTCAAGCTTTTGCCACAATTCGGCATCCAG  
AGCCCCGGCGCACAGAGCACAGGGNTCCTTTTTCAACGTGGCGACCAGTGGCCCTGACCCTG  
CTGACTTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTTTTTCAGTA  
CTACCAGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGATTAGGAAATA  
CGTCCCAAGAGTTGCAATTTNTTCAAGTCCAGAATATAAAGCTTGCAGGAAGTNTGCAGCAT  
GTGGCTGAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGGAACTTTGAAGGAGGGCAA  
AGTNTCCTCATNTACTATACACACACCACTTCCC

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**FIGURE 232**

GCCGAGCGCAAGAACCCTGCGCAGCCCAGAGCAGCTGCTGGAGGGGAATCGAGGCGCGGCTC  
CGGGGATTCTGGCTCGGGCCGCTGGCTCTGCTCTGCGGGGAGGGAGCGGGCCCCGCGGGG  
CCCGAGCCCTCCGGATCCGCCCCCTCCCCGGTCCCGCCCCCTCGGAGACTCCTCTGGCTGCT  
CTGGGGGTTCGCCGGGGGCCGGGGACCCGCGGTCCGGGGCGCCATGCGGGGCATCGCTGCTGCTG  
TCGGTGCTGCGGCCCCGAGGGCCCGTGGCCGTGGGCATCTCCCTGGGCTTCACCCTGAGCCT  
GCTCAGCGTCACCTGGGTGGAGGAGCCGTGCGGCCAGGCCCGCCCCAACCTGGAGACTCTG  
AGCTGCCGCCGCGCGGCAACACCAACGCGGCGCGCCGGGCCCAACTCGGTGCAGCCCGGAGCG  
GAGCGCGAGAAGCCCCGGGGCCGGCGAAGGCGCCGGGGAGAATTGGGAGCCGCGCGTCTTGCC  
CTACCACCCTGCACAGCCCGGCCAGGCCGCCAAAAGGCCGTGAGGACCCGCTACATCAGCA  
CGGAGCTGGGCATCAGGCAGAGGCTGCTGGTGGCGGTGCTGACCTCTCAGACCACGCTGCCC  
ACGCTGGGCGTGGCCGTGAACCGCACGCTGGGGCACCGGCTGGAGCGTGTGGTGTTCCTGAC  
GGGCGCACGGGGCCGCCGGGGCCCCACCTGGCATGGCAGTGGTGACGCTGGGCGAGGAGCGAC  
CCATTGGACACCTGCACCTGGCGCTGCGCCACCTGCTGGAGCAGCACGGCGACGACTTTGAC  
TGGTTCTTCCTGGTGCTGACACCACCTACACCGAGGCGCACGGCCTGGCACGCCTAACTGG  
CCACCTCAGCCTGGCCTCCGCCGCCACCTGTACCTGGGCCGGCCCCAGGACTTCATCGGCG  
GAGAGCCCACCCCCGGCCGCTACTGCCACGGAGGCTTTGGGGTGCTGCTGTCGCGCATGCTG  
CTGCAACAACCTGCGCCCCACCTGGAAGGCTGCCGCAACGACATCGTCAGTGCGCGCCCTGA  
CGAGTGGCTGGGTGCTGCATTCTCGATGCCACCGGGGTGGGCTGCACTGGTGACCACGAGG  
GGGTGCACTATAGCCATCTGGAGCTGAGCCCTGGGGAGCCAGTGCAAGGAGGGGGACCCTCAT  
TTCCGAAGTGCCCTGACAGCCCACCCTGTGCGTGACCCTGTGCACATGTACCAGCTGCACAA  
AGCTTTCGCCCCGAGCTGAACTGGAACGCACGTACCAGGAGATCCAGGAGTTACAGTGGGAGA  
TCCAGAATAACAGCCATCTGGCCGTTGATGGGGACCGGGCAGCTGCTTGGCCCCGTGGGTATT  
CCAGCACCATCCCGCCCCGGCCTCCCGCTTTGAGGTGCTGCGCTGGGACTACTTCACGGAGCA  
GCACGCTTTCTCCTGCGCCGATGGCTCACCCCGCTGCCCACTGCGTGGGGCTGACCGGGCTG  
ATGTGGCCGATGTTCTGGGGACAGCTCTAGAGGAGCTGAACCGCCGCTACCACCCGGCCTTG  
CGGCTCCAGAAGCAGCAGCTGGTGAATGGCTACCGACGCTTTGATCCGGCCCCGGGGTATGGA  
ATACACGCTGGACTTGCAGCTGGAGGCACTGACCCCCCAGGGAGGCCGCCGGCCCCCTCACTC  
GCCGAGTGCACTGCTCCGGCCGCTGAGCCGCGTGGAGATCTTGCCCTGTGCCCTATGTCACT  
GAGGCCTCACGTCTCACTGTGCTGCTGCCTCTAGCTGCGGCTGAGCGTGACCTGGCCCCCTGG  
CTTCTTGGAGGCCTTTGCCACTGCAGCACTGGAGCCTGGTGATGCTGCGGCAGCCCTGACCC  
TGCTGCTACTGTATGAGCCGCGCCAGGCCAGCGCGTGGCCCATGCAGATGTCTTCGCACCT  
GTCAAGGCCACGTGGCAGAGCTGGAGCGGCGTTTCCCCGGTGCCCGGGTGCCATGGCTCAG  
TGTGCAGACAGCCGCACCCTCACCCTGCGCCTCATGGATCTACTCTCCAAGAAGCACCCGC  
TGGACACACTGTTCTGCTGGCCGGGGCCAGACACGGTGCTCACGCCTGACTTCTGAACCGC  
TGCCGCATGCATGCCATCTCCGGCTGGCAGGCCTTCTTTCCCATGCATTTCCAAGCCTTCCA  
CCCAGGTGTGGCCCCACCACAAGGGCCTGGGCCCCCAGAGCTGGGCCGTGACACTGGCCGCT  
TTGATCGCCAGGCAGCCAGCGAGGCCTGCTTCTACAACTCCGACTACGTGGCAGCCCGTGGG  
CGCCTGGCGGCAGCCTCAGAACAAGAAGAGGAGCTGCTGGAGAGCCTGGATGTGTACGAGCT  
GTTCTTCCACTTCTCCAGTCTGCATGTGCTGCGGGCGGTGGAGCCGGCGCTGCTGCAGCGCT  
ACCGGGCCCAGACGTGCAGCGCGAGGCTCAGTGAGGACCTGTACCACCGCTGCCTCCAGAGC  
GTGCTTGAGGGCCTCCGGCTCCCGAACCAGCTGGCCATGCTACTCTTTGAACAGGAGCAGGG  
CAACAGCACCTGACCCCCACCCTGTCCCCGTGGGCCGTGGCATGGCCACACCCCCACCCACTT  
CTCCCCCAAACAGAGCCACCTGCCAGCCTCGCTGGGCAGGGCTGGCCGTAGCCAGACCCC  
AAGCTGGCCCACTGGTCCCCTCTCTGGCTCTGTGGGTCCCTGGGCTCTGGACAAGCACTGGG  
GGACGTGCCCCCAGAGCCACCCACTTCTCATCCCAAACCCAGTTTCCCTGCCCCCTGACGCT  
GCTGATTCTGGGCTGTGGCCTCCACGTATTTATGCAGTACAGTCTGCCTGACGCCAGCCCTGC  
CTCTGGGCCCTGGGGGCTGGGCTGTAGAAGAGTTGTTGGGGAAGGAGGGAGCTGAGGAGGGG  
GCATCTCCCAACTTCTCCCTTTTGGACCCTGCCGAAGCTCCCTGCCTTTAATAAACTGGCCA  
AGTGTGGAAAAA



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**FIGURE 233**

MRASLLLSVLRPAGPVAVGISLGFTLSLLSVTWVEEPCGPGPPQPGDSELPPRGNTNAARRP  
NSVQPGAEREKPGAGEGAGENWEPRVLPYHPAQPGQAACKAVRTRYISTELGIRQRLLVAVL  
TSQTTLPTLGVAVNRTLGHRLERVVFLTGARGRRAPPGMAVVTLGEERPIGHLHLALRHLL  
QHGDDEFDWFFLVPDTTYTEAHGLARLTGHLSLASAAHLYLGRPQDFIGGEPTPGRYCHGGFG  
VLLSRMLLQQLRPHLEGCRNDIVSARPDEWLGRCIL DATGVGCTGDHEGVHYSHLELSPGEP  
VQEGDPHFERSALTAHPVRDPVHMYQLHKAFARAELETTYQEIQELQWEIQNTSHLAVDGDRA  
AAWPVGIPAPSRPASRFEVLRWDYFTEQHAFSCADGSPRCPLRGADRADVADVLGTALEELN  
RRYHPALRLQKQQLVNGYRRFDPARGMEYTLDLQLEALTPQGGRRPLTRRVQLLRPLSRVEI  
LPVPYVTEASRLTVLLPLAAAERDLAPGFLEAFATAALEPGDAAAALTLLLLYEPRQAQRVA  
HADVFAPVKAHVAELERRFPGARVPWLSVQTAAPSPLRLMDLLSKKHPLDTLFLLAGPDTVL  
TPDFLNRCRMHAISGWQAFFPMHFQAFHPGVAPPQGGPGPPELGRDTGRFDRQAASEACFYNS  
DYVAARGRLAAASEQEEELLES LDVYELFLHFSSLHVLRAVEPALLQRYRAQTCSARLSEDL  
YHRCLQSVLEGLGSRTQLAMLLFEQE QGNST

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**FIGURE 234**

GCTCTGGCCGGCCCCGGCGATTGGTCACCGCCCGCTAGGGGACAGCCCTGGCCTCCTCTGAT  
TGGCAAGCGCTGGCCACCTCCCCACACCCCTTGCGAACGCTCCCCTAGTGGAGAAAAGGAGT  
AGCTATTAGCCAATTCGGCAGGGCCCGCTTTTTAGAAAGCTTGATTTCTTTGAAGATGAAAG  
ACTAGCGGAAGCTCTGCCTCTTTCCCCAGTGGGCGAGGGAACTCGGGGCGATTGGCTGGGAA  
CTGTATCCACCCAAATGTCACCGATTTCTTCCTATGCAGGAAATGAGCAGACCCATCAATAA  
GAAATTTCTCAGCCTGGCCGAAAATGGTTGGCCCCACGAAGCCACGACAACCTGGAGGCAAAG  
AGGGTTGCTCAACGCCCCGCCTCATTGGAAAACCAAATCAGATCTGGGACCTATATAGCGTG  
GCGGAGGCGGGGCGATGATTGTCGCGCTCGCACCCACTGCAGCTGCGCACAGTCGCATTTCT  
TTCCCCGCCCCCTGAGACCCTGCAGCACCATCTGTCAATGGCGGCTGGGCTGTTTGGTTTGAGC  
GCTCGCCGTCTTTTGGCGGCAGCGGCGACGCGAGGGCTCCCGGCCGCCCGCGTCCGCTGGGA  
ATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCTGTGGCGGGAAAGCGGCCCCCAGAAC  
CGACCACACCGTGGCAAGAGGACCCAGAACCCGAGGACGAAAACCTTGTATGAGAAGAACCCA  
GACTCCCATGGTTATGACAAGGACCCCGTTTTGGACGTCTGGAACATGCGACTTGTCTTCTT  
CTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACCTTTGTGGCCTATCTGCCTGACTACA  
GGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCTTGTGAAATACCGAGAGGCCAATGGC  
CTTCCCATCATGGAATCCAACCTGCTTCGACCCCAGCAAGATCCAGCTGCCAGAGGATGAGTG  
ACCAGTTGCTAAGTGGGGCTCAAGAAGCACCGCCTTCCCCACCCCCTGCCTGCCATTCTGAC  
CTCTTCTCAGAGCACCTAATTAAAGGGGCTGAAAGTCTGAA

**FIGURE 235**

MAAGLFGLSARRLLAAAATRGLPAARVRWESSFSRTVVAPSAVAGKRPPEPTTPWQEDPEPE  
DENLYEKNPDSHGYDKDPVLDVWNMRLVFFFGVSIILVLGSTFVAYLPDYRMKEWSRREAER  
LVKYREANGLPIMESNCFDPSKIQLPEDE

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**FIGURE 236**

GGCGGCTGGGCTGTTTGGTTTGAGCGCTCGCCGTCTTTTGGCGGCAGCGGCGACGCGAGGGC  
TCCCGGCCGCCCCGCGTCCGCTGGGAATCTAGCTTCTCCAGGACTGTGGTCGCCCCGTCCGCT  
GTGGCGGGAAAGCGGCCCCCAGAACCGACCAACCGTGGCAAGAGGACCCAGAACCCGAGGA  
CGAAAACCTTGATGAGAAGAACCAGACTCCCATGGTTATGACAAGGACCCCGTTTTGGACG  
TCTGGAACATGCGACTTGTCTTCTTCTTTGGCGTCTCCATCATCCTGGTCCTTGGCAGCACC  
TTTGTGGCCTATCTGCCTGACTACAGGATGAAAGAGTGGTCCCGCCGCGAAGCTGAGAGGCT  
TGTGAAATACCGAGAGGCCAATGGCCTTCCCATCATGGAATCCAACCTGCTTCGACCCCAGCA  
AGATCCAG



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**FIGURE 237**

GCGGCGGCTATGCCGCTTGCTCTGCTCGTCCTGTTGCTCCTGGGGCCCGGCGGCTGGTGCCCT  
TGCAGAACCCCCACGCGACAGCCTGCGGGAGGAACTTGTCATCACCCCGCTGCCTTCCGGGG  
ACGTAGCCGCCACATTCCAGTTCCGCACGCGCTGGGATTCGGAGCTTCAGCGGGAAGGAGTG  
TCCCATTACAGGCTCTTTCCCAAAGCCCTGGGGCAGCTGATCTCCAAGTATTCTCTACGGGA  
GCTGCACCTGTCATTACACAAGGCTTTTGGAGGACCCGATACTGGGGGGCCACCCTTCCTGC  
AGGCCCCATCAGGTGCAGAGCTGTGGGTCTGGTTCCAAGACACTGTCACTGATGTGGATAAA  
TCTTGGAAGGAGCTCAGTAATGTCCTCTCAGGGATCTTCTGCGCCTCTCTCAACTTCATCGA  
CTCCACCAACACAGTCACTCCCCTGCCTCCTTCAAACCCCTGGGTCTGGCCAATGACACTG  
ACCACTACTTTCTGCGCTATGCTGTGCTGCCGCGGGAGGTGGTCTGCACCGAAAACCTCACC  
CCCTGGAAGAAGCTCTTGCCCTGTAGTTCCAAGGCAGGCCTCTCTGTGCTGCTGAAGGCAGA  
TCGCTTGTTCCACACCAGCTACCACTCCCAGGCAGTGCATATCCGCCCTGTTTGCAGAAATG  
CACGCTGTACTAGCATCTCCTGGGAGCTGAGGCAGACCCTGTCAGTTGTATTTGATGCCTTC  
ATCACGGGGCAGGGAAAGAAAGACTGGTCCCTCTTCCGGATGTTCTCCCGAACCTCACGGA  
GCCCTGCCCCCTGGCTTCAGAGAGCCGAGTCTATGTGGACATCACCACTACAACCAGGACA  
ACGAGACATTAGAGGTGCACCCACCCCGACCACTACATATCAGGACGTCATCCTAGGCACT  
CGGAAGACCTATGCCATCTATGACTTGCTTGACACCGCCATGATCAACAACCTCTCGAAACCT  
CAACATCCAGCTCAAGTGGAAGAGACCCCGAGAGAATGAGGCCCCCCCCAGTGCCCTTCCTGC  
ATGCCCAGCGGTACGTGAGTGGCTATGGGCTGCAGAAGGGGGAGCTGAGCACACTGCTGTAC  
AACACCCACCCATACCGGGCCTTCCCGGTGCTGCTGCTGGACACCGTACCCTGGTATCTGCG  
GCTGTATGTGCACACCCTCACCATCACCTCCAAGGGCAAGGAGAACAACCAAGTTACATCC  
ACTACCAGCCTGCCCAGGACCGGCTGCAACCCACCTCCTGGAGATGCTGATTCAGCTGCCG  
GCCAACTCAGTCACCAAGGTTTCCATCCAGTTTGAGCGGGCGCTGCTGAAGTGGACCGAGTA  
CACGCCAGATCCTAACCATGGCTTCTATGTCAGCCCATCTGTCCTCAGCGCCCTTGTGCCCA  
GCATGGTAGCAGCCAAGCCAGTGGACTGGGAAGAGAGTCCCCTCTTCAACAGCCTGTTCCCA  
GTCTCTGATGGCTCTAACTACTTTGTGCGGCTCTACACGGAGCCGCTGCTGGTGAACCTGCC  
GACACCGGACTTCAGCATGCCCTACAACGTGATCTGCCTCACGTGCACTGTGGTGGCCGTGT  
GCTACGGCTCCTTCTACAATCTCCTCACCCGAACCTTCCACATCGAGGAGCCCCGCACAGGT  
GGCCTGGCCAAGCGGCTGGCCAACCTTATCCGGCGCGCCCGAGGTGTCCCCCCTCTGATT  
CTTGCCCTTTCCAGCAGCTGCAGCTGCCGTTTCTCTCTGGGGAGGGGAGCCCAAGGGCTGTT  
TCTGCCACTTGCTCTCCTCAGAGTTGGCTTTTGAACCAAAGTGCCCTGGACCAGGTGAGGC  
CTACAGCTGTGTTGTCCAGTACAGGAGCCACGAGCCAAATGTGGCATTGGAATTTGAATTAA  
CTTAGAAATTCATTTCTCACCTGTAGTGGCCACCTCTATATTGAGGTGCTCAATAAGCAAA  
AGTGGTCGGTGGCTGCTGTATTGGACAGCACAGAAAAAGATTTCCATCACACAGAAAGGTC  
GGCTGGCAGCACTGGCCAAGGTGATGGGGTGTGCTACACAGTGTATGTCACTGTGTAGTGGA  
TGGAGTTTACTGTTTGTGGAATAAAAACGGCTGTTTCCGTGGAAAAA

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**FIGURE 238**

MPLALLVLLLLGPGGWCLAEP PRDSLREELVITPLPSGDVAATFQFRTRWDSELQREGVSHY  
RLFPKALGQLISKYSLRELHLSFTQGFWRTRYWGPPFLQAPSGAELWVWFQDTVTDVDSWK  
ELSNVLSGIFCASLNFIDSTNTVTPTASF KPLGLANDTDHYFLRYAVLPREVVCTENLTPWK  
KLLPCSSKAGLSVLLKADRLFHTSYHSQAVHIRPVCRNARCTSI SWELRQTL SVVFD AFITG  
QGKKDWSLFRMFSRTLTEPCPLASESRVYVDITTYNQDNETLEVHPPPTTTYQDVILGTRKT  
YAIYDLLDTAMINNSRNLNIQLKWKRPPENEAPPVPFLHAQRYVSGYGLQKGELSTLLYNTH  
PYRAFPVLLLDTPWYLRLYVHTLTITSKGKENKPSYIHYQPAQDRLQPHLLEMLIQLPANS  
VTKVSIQFERALLKWTEYTPDPNHGFYVSPSVLSALVPSMVAAPVDWEESPLFNSLFPVSD  
GSNYFVRLYTEPLLVLNLPDPDFSMYPNVICLTCTVVAVCYGSFYNLLTRTFHIEEPRTGGLA  
KRLANLIRRARGVPPL

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**FIGURE 239**

CAACATGGGGTCCAGCAGCTTCTTGGTCCTCATGGTGTCTCTCGTTCTTGTGACCCTGGTGG  
CTGTGGAAGGAGTTAAAGAGGGTATAGAGAAAGCAGGGGTTTGCCCAGCTGACAACGTACGC  
TGCTTCAAGTCCGATCCTCCCCAGTGTACACAGACCAGGACTGTCTGGGGGAAAGGAAGTG  
TTGTTACCTGCACTGTGGCTTCAAGTGTGTGATTCCTGTGAAGGAACTGGAAGAAGGAGGAA  
ACAAGGATGAAGATGTGTCAAGGCCATACCCTGAGCCAGGATGGGAGGCCAAGTGTCCAGGC  
TCCTCCTCTACCAGGTGTCCTCAGAAATGATGCTGGGTCTTTTCTACCTCTGGGGGGTCACTC  
TCACTTGGCACCTGCCCCCTGAGGGTCCTGAGACTTGGAATATGGAAGAAGCAATACCCAACC  
CCACCAAAGAAAACCTGAGCTTGAAGTCCTTTTCCCCAAAAGAGGGAAGAGTCACAAAAG  
TCCAGACCCCAGGGACGGTACTTTCCCTCTCTACCTGGTGCTCCTCCCTAATGCTCATGAAT  
GGACCCCTCATGAATGAAACCAGTGCCCTTATAAGAGACCCCAAAGAGCTGCCTTGCCCTTC  
TGCAATGTGTGATCACAGCTAGAAGGCACTGTCAGAGAAGAGAACTGGTCCTCACCAGATG  
CTGAATCTGCTGGTGCCTTGATCTTGGACTTCCCAGCCTCTAGAACTGTAAGAAATAAATAT  
TTGCTGTTTATAATCCAA

**FIGURE 240**

MGSSSFLVLMVSLVLVTLVAVEGVKEGIEKAGVCPADNVRCFKSDPPQCHTDQDCLGERKCC  
YLHCGFKCVIPVKELEEGGNKDEDVSRPYPEPGWEAKCPGSSSTRCPQK



**FIGURE 241**

AAACTCAGCACTTGCCGGAGTGGCTCATTGTTAAGACAAAGGGTGTGCACTTCCTGGCCAGG  
AAACCTGAGCGGTGAGACTCCCAGCTGCCTACATCAAGGCCCCAGGACATGCAGAACCTTCC  
TCTAGAACCCGACCCACCACCAATGAGGTCTTGCCTGTGGAGATGCAGGCACCTGAGCCAAGG  
CGTCCAGTGGTCCTTGCTTCTGGCTGTCCTGGTCTTCTTTCTCTTCGCCTTGCCCTCTTTTA  
TTAAGGAGCCTCAAACAAAGCCTTCCAGGCATCAACGCACAGAGAACATTAAAGAAAGGTCT  
CTACAGTCCCTGGCAAAGCCTAAGTCCCAGGCACCCACAAGGGCGAGGAGGACAACCATCTA  
TGCAGAGCCAGCGCCAGAGAACAAATGCCCTCAACACACAAACCCAGCCCAAGGCCCACACCA  
CCGGAGACAGAGGAAAGGAGGCCAACCAGGCACCGCCGGAGGAGCAGGACAAGGTGCCCCAC  
ACAGCACAGAGGGCAGCATGGAAGAGCCCAGAAAAAGAGAAAACCATGGTGAACACACTGTC  
ACCCAGAGGGCAAGATGCAGGGATGGCCTCTGGCAGGACAGAGGCACAATCATGGAAGAGCC  
AGGACACAAAGACGACCCAAGGAAATGGGGGCCAGACCAGGAAGCTGACGGCCTCCAGGACG  
GTGTCAGAGAAGCACCAGGGCAAAGCGGCAACCACAGCCAAGACGCTCATTCCTCAAAAGTCA  
GCACAGAATGCTGGCTCCACAGGAGCAGTGTCAACAAGGACGAGACAGAAAGGAGTGACCA  
CAGCAGTCATCCACCTAAGGAGAAGAAACCTCAGGCCACCCCAACCCCTGCCCTTTCCAG  
AGCCCCACGACGCAGAGAAACCAAAGACTGAAGGCCGCCAACTTCAAATCTGAGCCTCGGTG  
GGATTTTGAGGAAAAATACAGCTTCGAAATAGGAGGCCTTCAGACGACTTGCCCTGACTCTG  
TGAAGATCAAAGCCTCCAAGTCGCTGTGGCTCCAGAACTCTTTCTGCCCAACCTCACTCTC  
TTCCTGGACTCCAGACACTTCAACCAGAGTGAGTGGGACCGCCTGGAACACTTTGCACCACC  
CTTTGGCTTCATGGAGCTCACTACTCCTTGGTGCAGAAGGTCTGTGACACGCTTCCCTCCAG  
TGCCCCAGCAGCAGCTGCTCCTGGCCAGCCTCCCCGCTGGGAGCCTCCGGTGATCACCTGT  
GCCGTGGTGGGCAACGGGGGCATCCTGAACAACTCCACATGGGCCAGGAGATAGACAGTCA  
CGACTACGTGTTCCGATTGAGCGGAGCTCTCATTAAAGGCTACGAACAGGATGTGGGGACTC  
GGACATCCTTCTACGGCTTTACCGCCTTCTCCCTGACCCAGTCACTCCTTATATTGGGCAAT  
CGGGGTTTCAAGAACGTGCCTCTTGGAAGGACGTCCGCTACTTGCACTTCCTGGAAGGCAC  
CCGGGACTATGAGTGGCTGGAAGCACTGCTTATGAATCAGACGGTGATGTCAAAAAACCTTT  
TCTGGTTCAGGCACAGACCCCAGGAAGCTTTTCGGGAAGCCCTGCACATGGACAGGTACCTG  
TTGCTGCACCCAGACTTTCTCCGATACATGAAGAACAGGTTTCTGAGGTCTAAGACCCTGGA  
TGGTGCCCACTGGAGGATATACCGCCCCACCACTGGGGCCCTCCTGCTGCTCACTGCCCTTC  
AGCTCTGTGACCAGGTGAGTGCTTATGGCTTCATCACTGAGGGCCATGAGCGCTTTTCTGAT  
CACTACTATGATACATCATGGAAGCGGCTGATCTTTTACATAAACCATGACTTCAAGCTGGA  
GAGAGAAGTCTGGAAGCGGCTACACGATGAAGGGATAATCCGGCTGTACCAGCGTCCTGGTC  
CCGGAAGTGCCAAAGCCAAGAACTGAACCGGGGCCAGGGCTGCCATGGTCTCCTTGCCCTGCTC  
CAAGGCACAGGATACAGTGGGAATCTTGAGACTCTTTGGCCATTTCCCATGGCTCAGACTAA  
GCTCCAAGCCCTTCAGGAGTTCCAAGGGAACACTTGAACCATGGACAAGACTCTCTCAAGAT  
GGCAAATGGCTAATTGAGGTTCTGAAGTTCTTCAGTACATTGCTGTAGGTCTTGAGGCCAGG  
GATTTTTTAATTAAATGGGGTGATGGGTGGCCAATACCACAATTCTTGCTGAAAAACACTCTT  
CCAGTCCAAAAGCTTCTTGATACAGAAAAAAGAGCCTGGATTTACAGAAACATATAGATCTG  
GTTTGAATTCCAGATCGAGTTTACAGTTGTGAAATCTTGAAGGTATTACTTAACTTCACTAC  
AGATTGTCTAGAAGACCTTTCTAGGAGTTATCTGATTCTAGAAGGGTCTATACTTGTCTTG  
TCTTTAAGCTATTTGACAACTCTACGTGTTGTAGAAAACCTGATAATAATACAAATGATTGTT  
GTCCATGGAAAGGCAAATAAATTTTCTACAGTGAAAAA

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**FIGURE 242**

MRSCLWRCRHL SQGVQWSLLLAVLVFFLFALPSFIKEPQTKPSRHRQRTENIKERSLQSLAKP  
KSQAPTRARRTTIYAEPAPENNALNTQTQPKAHTTGDRGKEANQAPPEEQDKVPHTAQRAAW  
KSPEKEKTMVNTLS PRGQDAGMASGRTEAQSWKSQDTKTTQGNGGQTRKLTASRTVSEKHQG  
KAATTAKTLIPKSQHRMLAPTGA VSTRTRQKGVTTAVIPPEKKPQATPPPAPFQSPTTQRN  
QRLKAANFKSEPRWDFEEKYSFEIGGLQTTCPDSVKIKASKSLWLQKLFLPNLTLFLDSRHF  
NQSEWDRLEHFAPPFGFMELNYSLVQKVVT RFPPVPQQQLLLASLPAGSLRCITCAVVGNGG  
ILNNSHMGQEIDSHDYVFRLSGALIKGYEQDVGTRTSFYGF TAFSLTQSLILGNRGFKNVP  
LGKDVRYLHFLEGTRDYEWLEALLMNQTVMSKNLFWFRHRPQEAFREALHMDRYLLLHPDFL  
RYMKNRFLRSKTL DGAHWRIYRPTTGALLLLTALQLCDQVSAYGFITEGHERFSDHYDTSW  
KRLIFYINHDFKLEREVWKRLHDEGIIRLYQRPGPGTAKAKN

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**FIGURE 243**

CGATGCGCGGACCCGGGCACCCCCTCCTCCTGGGGCTGCTGCTGGTGCTGGGGCCTTCGCCG  
GAGCAGCGAGTGGAAATTGTTCCCTCGAGATCTGAGGATGAAGGACAAGTTTCTAAAACACCT  
TACAGGCCCTCTTTATTTTAGTCCAAAGTGCAGCAAACACTTCCATAGACTTTATCACAACA  
CCAGAGACTGCACCATTCTGTCATACTATAAAAGATGCGCCAGGCTTCTTACCCGGCTGGCT  
GTCAGTCCAGTGTGCATGGAGGATAAGTGAGCAGACCGTACAGGAGCAGCACACCAGGAGCC  
ATGAGAAGTGCCTTGGAACCAACAGGGAAACAGAACTATCTTTATACACATCCCCTCATGG  
ACAAGAGATTTATTTTTTGCAGACAGACTCTTCCATAAGTCCTTTGAGTTTTGTATGTTGTTG  
ACAGTTTGCAGATATATATTCGATAAATCAGTGTACTTGACAGTGTTATCTGTCACTTATTT

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**FIGURE 244**

MRGPGHPLLLGLLLVLGPSPEQRVEIVPRDLRMKDKFLKHLTGPLYFSPKCSKHFHRLYHNT  
RDCTIPAYYKRCARLLTRLAVSPVCMEDK



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**FIGURE 245**

GGGCTGGGCCCCGCGCAGCTCCAGCTGGCCGGCTTGGTCCTGCGGTCCCTTCTCTGGGAGG  
CCCGACCCCGGCGCGCCAGCCCCACCATGCCACCCGCGGGGCTCCGCCGGGCGCGCCG  
CTCACCGCAATCGCTCTGTTGGTGCTGGGGGCTCCCCTGGTGCTGGCCGGCGAGGACTGCCT  
GTGGTACCTGGACCGGAATGGCTCCTGGCATCCGGGGTTTAACTGCGAGTTCTTCACCTTCT  
GCTGCGGGACCTGCTACCATCGGTACTGCTGCAGGGACCTGACCTTGCTTATCACCGAGAGG  
CAGCAGAAGCACTGCCTGGCCTTCAGCCCCAAGACCATAGCAGGCATCGCCTCAGCTGTGAT  
CCTCTTTGTTGCTGTGGTTGCCACCACCATCTGCTGCTTCCTCTGTTCTTGCTACCTGT  
ACCGCCGGCGCCAGCAGCTCCAGAGCCCATTGAAGGCCAGGAGATTCCAATGACAGGCATC  
CCAGTGCAGCCAGTATACCCATACCCCCAGGACCCCAAAGCTGGCCCTGCACCCCCACAGCC  
TGGCTTCATGTACCCACCTAGTGGTCCTGCTCCCCAATATCCACTCTACCCAGCTGGGCCCC  
CAGTCTACAACCCTGCAGCTCCTCCTCCCTATATGCCACCACAGCCCTCTTACCCGGGAGCC  
TGAGGAACCAGCCATGTCTCTGCTGCCCCCTTCAGTGATGCCAACCTTGGGAGATGCCCTCAT  
CCTGTACCTGCATCTGGTCCTGGGGGTGGCAGGAGTCCTCCAGCCACCAGGCCCCAGACCAA  
GCCAAGCCCTGGGCCCTACTGGGGACAGAGCCCCAGGGAAGTGGAACAGGAGCTGAACTAGA  
ACTATGAGGGGTTGGGGGGAGGGCTTGGAATTATGGGCTATTTTACTGGGGGCAAGGGAGG  
GAGATGACAGCCTGGGTCACAGTGCCTGTTTTCAAATAGTCCCTCTGCTCCCAAGATCCCAG  
CCAGGAAGGCTGGGGCCCTACTGTTTGTCCCCTCTGGGCTGGGGTGGGGGGAGGGAGGAGGT  
TCCGTCAGCAGCTGGCAGTAGCCCTCCTCTCTGGCTGCCCCACTGGCCACATCTCTGGCCTG  
CTAGATTAAAGCTGTAAAGACAAAA

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**FIGURE 246**

MPPAGLRRRAAPLTAIALLVLGAPLVLAGEDCLWYLDRNGSWHPGFNCEFFTFCCGTCTYHRYC  
CRDLTLLITERQQKHCLAFSPKTIAGIASAVILFVAVVATTICCFLLCSCCYLYRRRQQQLQSP  
FEGQEIPMTGIPVQPVYPYPQDPKAGPAPPQPGFMYPPSGPAPQYPLYPAGPPVYNPAAPP  
YMPPQPSYPGA

**FIGURE 247**

GGGGGAGCTAGGCCGGCGGCAGTGGTGGTGGCGGCGGCGCAAGGGTGAGGGCGGCCCCAGAA  
CCCCAGGTAGGTAGAGCAAGAAGATGGTGTCTTCTGCCCCCTCAAATGGTCCCTTGCAACCATG  
TCATTTCTACTTTCTCTCACTGTTGGCTCTCTTAAGTGTGTCCACTCCTTCATGGTGTGAGAG  
CACTGAAGCATCTCCAAAACGTAGTGATGGGACACCATTTCCTTGGAATAAAATACGACTTC  
CTGAGTACGTATCCCAGTTCATTATGATCTCTTGATCCATGCAAACCTTACCACGCTGACC  
TTCTGGGGAACACGAAAGTAGAAATCACAGCCAGTCAGCCCACCAGCACCATCATCCTGCA  
TAGTCACCACCTGCAGATATCTAGGGCCACCCTCAGGAAGGGAGCTGGAGAGAGGCTATCGG  
AAGAACCCCTGCAGGTCTTGGAACACCCCCCTCAGGAGCAAATTGCACTGCTGGCTCCCGAG  
CCCCTCCTTGTGCGGGCTCCCGTACACAGTTGTCACTTCACTATGCTGGCAATCTTTTCGGAGAC  
TTTCCACGGATTTTACAAAAGCACCTACAGAACCAAGGAAGGGGAAGTGAAGGATACTAGCAT  
CAACACAATTTGAACCCACTGCAGCTAGAATGGCCTTTCCCTGCTTTGATGAACCTGCCTTC  
AAAGCAAGTTTCTCAATCAAAATTAGAAGAGAGCCAAGGCACCTAGCCATCTCCAATATGCC  
ATTGGTGAAATCTGTGACTGTTGCTGAAGGACTCATAGAAGACCATTTTGATGTCACTGTGA  
AGATGAGCACCTATCTGGTGGCCTTCATCATTTCAGATTTTGAGTCTGTGAGCAAGATAACC  
AAGAGTGGAGTCAAGGTTTCTGTTTATGCTGTGCCAGACAAGATAAATCAAGCAGATTATGC  
ACTGGATGCTGCGGTGACTCTTCTAGAATTTTATGAGGATTATTTTCAGCATACCGTATCCCC  
TACCCAAACAAGATCTTGCTGCTATTCCCGACTTTTCAGTCTGGTGCTATGGAAAAGTGGGGA  
CTGACAACATATAGAGAATCTGCTCTGTTGTTTGATGCAGAAAAGTCTTCTGCATCAAGTAA  
GCTTGGCATCACAGTGACTGTGGCCCATGAACTGGCCACCAGTGGTTTGGGAACCTGGTCA  
CTATGGAATGGTGGAAATGATCTTTGGCTAAATGAAGGATTTGCCAAATTTATGGAGTTTGTG  
TCTGTGAGTGTGACCCATCCTGAACTGAAAGTTGGAGATTATTTCTTTGGCAAATGTTTTGA  
CGCAATGGAGGTAGATGCTTTAAATTCCTCACACCCTGTGTCTACACCTGTGGAAAATCCTG  
CTCAGATCCGGGAGATGTTTGATGATGTTTCTTATGATAAGGGAGCTTGTATTCTGAATATG  
CTAAGGGAGTATCTTAGCGCTGACGCATTTAAAAGTGGTATTGTACAGTATCTCCAGAAGCA  
TAGCTATAAAAATACAAAAAACGAGGACCTGTGGGATAGTATGGCAAGTATTTGCCCTACAG  
ATGGTGTAAGGGATGGATGGCTTTTGCTCTAGAAGTCAACATTCATCTTCATCCTCACAT  
TGGCATCAGGAAGGGGTGGATGTGAAAACCATGATGAACACTTGGACACTGCAGAGGGGTTT  
TCCCCTAATAACCATCACAGTGAGGGGGAGGAATGTACACATGAAGCAAGAGCACTACATGA  
AGGGCTCTGACGGCGCCCCGGACACTGGGTACCTGTGGCATGTTCCATTGACATTCATCACC  
AGCAAATCCAACATGGTCCATCGATTTTGTCTAAAAACAAAAACAGATGTGCTCATCCTCCC  
AGAAGAGGTGGAATGGATCAAATTTAATGTGGGCATGAATGGCTATTACATTGTGCATTACG  
AGGATGATGGATGGGACTCTTTGACTGGCCTTTTAAAAGGAACACACACAGCAGTCAGCAGT  
AATGATCGGGCAAGTCTCATTAACAATGCATTTTCAGCTCGTCAGCATTGGGAAGCTGTCCAT  
TGAAAAGGCCTTGGATTTATCCCTGTACTTGAAACATGAACTGAAATTATGCCCCGTGTTTC  
AAGGTTTGAATGAGCTGATTCCCTATGTATAAGTTAATGGAGAAAAGAGATATGAATGAAGTG  
GAACTCAATTCAAGGCCTTCCTCATCAGGCTGCTAAGGGACCTCATTGATAAGCAGACATG  
GACAGACGAGGGCTCAGTCTCAGAGCAAATGCTGCGGAGTGAACACTACTCCTCGCCTGTG  
TGCACAACATATCAGCCGTGCGTACAGAGGGCAGAAGGCTATTTTCAGAAAGTGGAAAGGAATCC  
AATGGAACTTGAGCCTGCCTGTGACGTGACCTTGGCAGTGTGTTGCTGTGGGGGGCCAGAG  
CACAGAAGGCTGGGATTTTCTTTATAGTAAATATCAGTTTTTCTTTGTCCAGTACTGAGAAAA  
GCCAAATTGAATTTGCCCTCTGCAGAACCCAAAATAAGGAAAAGCTTCAATGGCTACTAGAT  
GAAAGCTTTAAGGGAGATAAAAATAAAACTCAGGAGTTTCCACAAATTCTTACACTCATTGG  
CAGGAACCCAGTAGGATACCCACTGGCCTGGCAATTTCTGAGGAAAACTGGAACAACTTG  
TACAAAAGTTTGAACCTTGGCTCATCTTCCATAGCCACATGGTAATGGGTACAACAAATCAA  
TTCTCCACAAGAACACGGCTTGAAGAGGTAAAAGGATTCTTCAGCTCTTTGAAAGAAAATGG  
TTCTCAGCTCCGTGTGTCCAACAGACAATTGAAACCATTGAAGAAAACATCGGTTGGATGG  
ATAAGAATTTTGATAAAATCAGAGTGTGGCTGCAAAGTGAAAAGCTTGAACGTATGTAAAAA  
TTCCTCCCTTGCCCGGTTCTGTTATCTCTAATCACCAACATTTTGTGAGTGTATTTTCAA  
ACTAGAGATGGCTGTTTTGGCTCCAACCTGGAGATACTTTTTTCCCTTCAACTCATTTTTTGA  
CTATCCCTGTGAAAAGAATAGCTGTTAGTTTTTCATGAATGGGCTTTTTTCATGAATGGGCTA  
TCGCTACCATGTGTTTTGTTTCATCACAGGTGTTGCCCTGCAACGTAAACCCAAGTGTTGGGT  
TCCCTGCCACAGAAGAATAAAGTACCTTATTCTTCTCAAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 248**

MVFLPLKWSLATMSFLLSSLALLTVSTPSWCQSTEASPKRSDGTPFPWNKIRLPEYVIPVH  
YDLLIHANLTTLTFWGTTKVEITASQPTSTIILHSHHLQISRATLRKGAGERLSEEPLQVLE  
HPPQEQIALLAPEPLLVGLPYTVVIHYAGNLSETFHGFYKSTYRTKEGELRILASTQFEPTA  
ARMAFPCFDEPAFKASF SIKIRREPRHLAISNMPLVKSVTVAEGLIEDHFDVTVKMSTYLVA  
FIISDFESVSKITKSGVKVSVYAVPDKINQADYALDAAVTLLEFYEDYFSIPYPLPKQDLAA  
IPDFQSGAMENWGLTTYRESALLFDAEKSSASSKLGITVTVAHELAHQWFGNLVTMEWWNDL  
WLNEGFAKFMEFVSVSVTHPELKVG DYFFGKCFDAMEVDALNSSHPVSTPVENPAQIREMFD  
DVSYDKGACILNMLREYLSADAFKSGIVQYLQKHSYKNTKNEDLWDSMASICPTDGVKGM DG  
FCSRSQHSSSSSHWHQEGVDVKTMMNTWTLQRGFPLITITVRGRNVHMKQEHYMKGSDGAPD  
TGYLWHVPLTFITSKSNMVHRFLLKTKTDVLILPEEVEWIKFNVGMNGYYIVHYEDDGWDSL  
TGLLKGTHTAVSSNDRASLINNAFQLVSIGKLSIEKALDLSLYLKHETEIMPVFQGLNELIP  
MYKLMEKRD MNEVETQFKAFLIRLLRDLIDKQTTWTDEGSVSEQMLRSELLLLACVHNYQPCV  
QRAEGYFRKWKESNGNLSLPVDVTLAVFAVGAQSTEGWDFLYSKYQFSLSSTEKSQIEFALC  
RTQNKEKLQWLLDESFKGDKIKTQEF PQILTLIGRNPVGYPLAWQFLRKNWNKLVQKFELGS  
SSIAHMVMGTTNQFSTRTRLEEVKGFFSSLKENGSQLRCVQQT IETIEENIGWMDKNFDKIR  
VWLQSEKLERM



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**FIGURE 249**

CAGCCACAGACGGGTCATGAGCGCGGTATTACTGCTGGCCCTCCTGGGGTTCATCCTCCCAC  
TGCCAGGAGTGCAGGCGCTGCTCTGCCAGTTTGGGACAGTTCAGCATGTGTGGAAGGTGTCC  
GACCTACCCCGGCAATGGACCCCTAAGAACACCAGCTGCGACAGCGGCTTGGGGTGCCAGGA  
CACGTTGATGCTCATTGAGAGCGGACCCCAAGTGAGCCTGGTGCTCTCCAAGGGCTGCACGG  
AGGCCAAGGACCAGGAGCCCCGCGTCACTGAGCACCGGATGGGCCCCGGCCTCTCCCTGATC  
TCCTACACCTTCGTGTGCCGCCAGGAGGACTTCTGCAACAACCTCGTTAACTCCCTCCCGCT  
TTGGGCCCCACAGCCCCCAGCAGACCCAGGATCCTTGAGGTGCCCAGTCTGCTTGTCTATGG  
AAGGCTGTCTGGAGGGGACAACAGAAGAGATCTGCCCCAAGGGGACCACACACTGTTATGAT  
GGCCTCCTCAGGCTCAGGGGAGGAGGCATCTTCTCCAATCTGAGAGTCCAGGGATGCATGCC  
CCAGCCAGGTTGCAACCTGCTCAATGGGACACAGGAAATTGGGCCCCGTGGGTATGACTGAGA  
ACTGCAATAGGAAAGATTTTCTGACCTGTCATCGGGGGACCACCATTATGACACACGGAAAC  
TTGGCTCAAGAACCCACTGATTGGACCACATCGAATACCGAGATGTGCGAGGTGGGGCAGGT  
GTGTCAGGAGACGCTGCTGCTCATAGATGTAGGACTCACATCAACCCTGGTGGGGACAAAAG  
GCTGCAGCACTGTTGGGGCTCAAAATTCCCAGAAGACCACCATCCACTCAGCCCCCTCCTGGG  
GTGCTTGTGGCCTCCTATACCCACTTCTGCTCCTCGGACCTGTGCAATAGTGCCAGCAGCAG  
CAGCGTTCTGCTGAACTCCCTCCCTCCTCAAGCTGCCCCCTGTCCCAGGAGACCGGCAGTGTC  
CTACCTGTGTGCAGCCCCCTTGGAACCTGTTCAAGTGGCTCCCCCGAATGACCTGCCCCAGG  
GGCGCCACTCATTGTTATGATGGGTACATTCATCTCTCAGGAGGTGGGCTGTCCACCAAAT  
GAGCATTCAAGGCTGCGTGGCCCAACCTTCCAGCTTCTTGTTGAACCACACCAGACAAATCG  
GGATCTTCTCTGCGCGTGAGAAGCGTGATGTGCAGCCTCCTGCCTCTCAGCATGAGGGAGGT  
GGGGCTGAGGGCCTGGAGTCTCTCACTTGGGGGGTGGGGCTGGCACTGGCCCCAGCGCTGTG  
GTGGGGAGTGGTTTGCCCTTCCTGCTTAACTCTATTACCCCCACGATTCTTCACCGCTGCTGA  
CCACCCACACTCAACCTCCCTCTGACCTCATAACCTAATGGCCTTGGACACCAGATTCTTTC  
CCATTCTGTCCATGAATCATCTTCCCCACACACAATCATTATATCTACTCACCTAACAGCA  
ACACTGGGGAGAGCCTGGAGCATCCGGACTTGCCCTATGGGAGAGGGGACGCTGGAGGAGTG  
GCTGCATGTATCTGATAATACAGACCCTGTCCTTTCA

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**FIGURE 250**

MSAVLLLALLGFILPLPGVQALLCQFGTVQHVWKVSDLPRQWTPKNTSCDSGLGCQDTLMLI  
ESGPQVSLVLSKGCTEAKDQEPRVTEHRMGPGLSLISYTFVCRQEDFCNNLVNSLPLWAPQP  
PADPGSLRCPVCLSMEGCLEGTTEEICPKGTTHCYDGLLRRLRGGGIFSNLRVQGCMPQPGCN  
LLNGTQEIGPVGMTENCNRKDFLTCHRGTTIMTHGNLAQEPTDWTTSNTEMCEVGQVCQETL  
LLIDVGLTSTLVGTKGCSTVGAQNSQKTTIHSAPPGVLVASYTHFCSSDLCNSASSSSVLLN  
SLPPQAAPVPGDRQCPTCVQPLGTCSSGSPRMTCPRGATHCYDGYIHLSGGGLSTKMSIQGC  
VAQPSSFLLNHTRQIGIFSAREKRDVQPPASQHEGGGAEGLESLTWGVGLALAPALWWGVVCPSC

**FIGURE 251**

GCGACGGGCAGGACGCCCCGTTTCGCCTAGCGCGTGCTCAGGAGTTGGTGTCTGCTGCGCT  
CAGGATGAGGGGGAATCTGGCCCTGGTGGGCGTTCTAATCAGCCTGGCCTTCCTGTCACTGCTG  
CCATCTGGACATCCTCAGCCGGCTGGCGATGACGCCTGCTCTGTGCAGATCCTCGTCCCTGG  
CCTCAAAGGGGATGCGGGAGAGAAGGGAGACAAAGGCGCCCCCGGACGGCCTGGAAGAGTCG  
GCCCCACGGGAGAAAAAGGAGACATGGGGGACAAAGGACAGAAAGGCAGTGTGGGTCGTCA  
TGAAAAATTGGTCCCATTTGGCTCTAAAGGTGAGAAAGGAGATTCCGGTGACATAGGACCCCC  
TGGTCCTAATGGAGAACCAGGCCTCCCATGTGAGTGCAGCCAGCTGCGCAAGGCCATCGGGG  
AGATGGACAACCAGGTCTCTCAGCTGACCAGCGAGCTCAAGTTCATCAAGAATGCTGTGCC  
GGTGTGCGCGAGACGGAGAGCAAGATCTACCTGCTGGTGAAGGAGGAGAAGCGCTACGCGGA  
CGCCCAGCTGTCCTGCCAGGGCCGCGGGGGCACGCTGAGCATGCCCAAGGACGAGGCTGCCA  
ATGGCCTGATGGCCGCATACCTGGCGCAAGCCGGCCTGGCCCGTGTCTTCATCGGCATCAAC  
GACCTGGAGAAGGAGGGCGCCTTCGTGTACTCTGACCACTCCCCCATGCGGACCTTCAACAA  
GTGGCGCAGCGGTGAGCCCAACAATGCCTACGACGAGGAGGACTGCGTGGAGATGGTGGCCT  
CGGGCGGCTGGAACGACGTGGCCTGCCACACCACCATGTACTTCATGTGTGAGTTTGACAAG  
GAGAACATGTGAGCCTCAGGCTGGGGCTGCCCATTTGGGGGCCCCACATGTCCCTGCAGGGTT  
GGCAGGGACAGAGCCCAGACCATGGTGCCAGCCAGGGAGCTGTCCCTCTGTGAAGGGTGGAG  
GCTCACTGAGTAGAGGGCTGTTGTCTAAACTGAGAAAATGGCCTATGCTTAAGAGGAAAATG  
AAAGTGTTCCCTGGGGTGCTGTCTCTGAAGAAGCAGAGTTTCATTACCTGTATTGTAGCCCCA  
ATGTCATTATGTAATTATTACCCAGAATTGCTCTTCCATAAAGCTTGTGCCTTTGTCCAAGC  
TATACAATAAAATCTTTAAGTAGTGCAGTAGTTAAGTCCAAAAAAAAAAAAAAAAAAAAA

**FIGURE 252**

MRGNLALVGVLISLAFLLPSGHPQPAGDDACSVQILVPGLKGDAGEKGDKGAPGRPGRVG  
PTGEKGDMGDKGQKGSVGRHGKIGPIGSKGEKGDSDIGPPGPNGEPGLPCECSQLRKAIGE  
MDNQVSQLTSELKFIKNAVAGVRETESKIYLLVKEEKRYADAQLSCQGRGGTLSMPKDEAAN  
GLMAAYLAQAGLARVFIGINDLEKEGAFVYSDHSPMRTFNKWRSGEPNNAYDEEDCVEMVAS  
GGWNDVACHTTMYFMCEFDKENM



**FIGURE 253**

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTGCAGGAGCACCGGCAG  
CACCAGTGTGTGAGGGGAGCAGGCAGCGGTCCTAGCCAGTTCCTTGATCCTGCCAGACCACC  
CAGCCCCCGGCACAGAGCTGCTCCACAGGCACCATGAGGATCATGCTGCTATTACAGCCAT  
CCTGGCCTTCAGCCTAGCTCAGAGCTTTGGGGCTGTCTGTAAGGAGCCACAGGAGGAGGTGG  
TTCCTGGCGGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCAGAGACTCTTC  
AAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAGCACAGATCCTAA  
GGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGGACTTATGGGCAAGA  
GGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGTGAGGGTTCCTCGGCCC  
CTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGGAACAGAGGAGCAGAGACC  
TTTATAAGACTCTCCTACGGATGTGAATCAAGAGAACGTCCCCAGCTTTGGCATCCTCAAGT  
ATCCCCCGAGAGCAGAATAGGTACTCCACTTCCGGACTCCTGGACTGCATTAGGAAGACCTC  
TTTCCCTGTCCCAATCCCCAGGTGCGCACGCTCCTGTTACCCTTTCTCTTCCCTGTTCTTGT  
AACATTCTTGTGCTTTGACTCCTTCTCCATCTTTTCTACCTGACCCTGGTGTGGAAACTGCA  
TAGTGAATATCCCCAACCCCAATGGGCATTGACTGTAGAATACCCTAGAGTTCCTGTAGTGT  
CCTACATTAAAAATATAATGTCTCTCTCTATTCTCAACAATAAAGGATTTTTGCATATGAA  
AA

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**FIGURE 254**

MRIMLLFTAILAFSLAQSFQAVCKEPQEEVPPGGGRSKRDPDLYQLLQRLFKSHSSLEGLLK  
ALSQASTDPKESTSPEKRDMHDFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLGSTGK  
SSLGTEEQRPL

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**FIGURE 255**

GGGCGTCTCCGGCTGCTCCTATTGAGCTGTCTGCTCGCTGTGCCCGCTGTGCCTGCTGTGCC  
CGCGCTGTCGCCGCTGCTACCGCGTCTGCTGGACGCGGGAGACGCCAGCGAGCTGGTGATTG  
GAGCCCTGCGGAGAGCTCAAGCGCCCAGCTCTGCCCCAGGAGCCCAGGCTGCCCCGTGAGTC  
CCATAGTTGCTGCAGGAGTGGAGCCATGAGCTGCGTCCTGGGTGGTGTTCATCCCCTTGGGGC  
TGCTGTTCTTGGTCTGCGGATCCCAAGGCTACCTCCTGCCCAACGTCACTCTCTTAGAGGAG  
CTGCTCAGCAAATACCAGCACAAACGAGTCTCACTCCCGGGTCCGCAGAGCCATCCCCAGGGA  
GGACAAGGAGGAGATCCTCATGCTGCACAACAAGCTTCGGGGCCAGGTGCAGCCTCAGGCCT  
CCAACATGGAGTACATGGTGAGCGCCGGCTCCGGCCGCAGAGGCTGGCACCGGGGGTGGGGC  
CTGGGCCACCAGCCTGCTCTGTTCCCCAGCCAGCTCTGTTCCCCAGCCAGTGCGTGTGATGG  
CTGGCTCAGGGTCTCCTCTGGCAGGGGAGGATCCCGGCTCTGTTCTGTTTTGTTTGTGTTGTT  
TTGAGACAGGGTCTCACTCTGCCACTGACGCTGGAGTGCAATGGCACAATCGTCATGCCCTG  
AAACCTTAGACTCCCGGGGTTAAGCGATCCTGCTTCAGCCTCCCAAGTAGCTGGAACCTACAG  
GCATGCACCATGGTGCCAGCTAGATTTTAAATATTTTGTGGAGATGGGGGTCTTGCTACGT  
TGCCCAGGCTGGTCTTGAACTCCTAGGCTCAAGCAATCCTCCTGCCTCAGCCTCTCAAAGTG  
CTAGGATTATAGGCATGAGTCACCCTGTCTGGCTCTGGCTCTGTTCTTAACATTCTGCCAAA  
ACAACACACGTGGGTTCCTGTGCAGAGCCTGCCTCGTTGCCTTCATGTCACTCTTGGTAGC  
TCCACTGGGAACACAGCTCTCAGCCTTTCCCACCTGGAGGCAGAGTGGGGAGGGGCCCAGGG  
CTGGGCTTTGCTGATGCTGATCTCAGCTGTGCCACACGCTAGCTGCACCACCCTGACTTCTC  
CTTAGCCCGTGTGAGCCTCACTTTCCACTTGGAGAGTCCTTCCTCGCGTGGTTGCCATGACT  
GTGAGATAAGTCGAGGCTGTGAAGGGCCCGGCACAGACTGACCTGCCTCCCCAACCCCTAGG  
CTTTGCTAACCGGGAAAGGAGCTAACGGTGACAGAAGACAGCCAAGGTCAACCCTCCCGGGT  
GATTGTGATGGGTGTTCCAGGTGTGGTTGGGCGATGCTGCTACTTGACCCCAAGCTCCAGTG  
TGGAACCTTCCTTCCTGGCTGGTTTTCCAGAACTACAGAGGAATGGACCACAGTCTTCCAGG  
GTCCCTCCTCGTCCACCAACCGGGAGCCTCCACCTTGGCCATCCGTCAGCTATGAATGGCTT  
TTTAAACAAACCCACGTCCCAGCCTGGGTAACATGGTAAAGCCCCGTCTCTACAAAAAATC  
CAAGTTAGCCGGGCATGGTGGTGCGCACCTGTAGTCCCAGCTGCAGTGGGACTGAGGTGGAG  
GTGGAGGTGGGGGGTGGGAGCTGAGGAAGGAGGATCGCTTGAGCCTGGGAAGTCGAGGCTGC  
AGTGAGCTGAGATTGCACCACTGCACTCCAGCCTGGGTGACAGAGCAAGACCCTGTCTCAAAAA

**FIGURE 256**

MSCVLGGV IPLGLLFLVCGSQGYLLPNVTLLLEELLSKYQHNEHSRVRRAIPREDKEEILML  
HNKLRGQVQPQASNMEYMSAGSGRRGWHRGWGLGHQPALFPSQLCSPASACDGLRVSSGR  
GGSRLCSVLFVCFETGSHSATDAGVQWHNRHALKP



**FIGURE 257**

AAGGAGAGGCCACCGGGACTTCAGTGTCTCCTCCATCCCAGGAGCGCAGTGGCCACTATGGG  
GTCTGGGCTGCCCCCTTGTCCTCCTCTTGACCCTCCTTGGCAGCTCACATGGAACAGGGCCGG  
GTATGACTTTGCAACTGAAGCTGAAGGAGTCTTTTCTGACAAATTCCTCCTATGAGTCCAGC  
TTCCTGGAATTGCTTGAAAAGCTCTGCCTCCTCCTCCATCTCCCTTCAGGGACCAGCGTCAC  
CCTCCACCATGCAAGATCTCAACACCATGTTGTCTGCAACACATTGACAGCCATTGAAGCCTG  
TGTCTTCTTGGCCCCGGGCTTTTGGGCCGGGGATGCAGGAGGCAGGCCCCGACCCTGTCTTT  
CAGCAGGCCCCCACCCTCCTGAGTGGCAATAAATAAAATTCGGTATGCTG

**FIGURE 258**

MSGGLPLVLLLTLGSSHGTGPGMTLQLKLKESFLTNSSESSFLELLEKLCLLLHLPSGTS

·VTLHHARSQHHVVCNT

**FIGURE 259**

AATTGTATCTGTGTAATGTTAAAACAAACGAAATAAAATAGAAGGAAAAACTTTCTGAGTTT  
CAAAAACAACAGACTAGTACTCTAAAGAACTCTTTAAAACAATTAAGTGTAGGATTGCAGT  
TATGATTGGATATTATTTAATTCTGTTTCTGATGTGGGGTTCCTCCACTGTGTTCTGTGTGC  
TATTAATATTTACCATTGCAGAAGCTTCATTCAGTGTTGAAAATGAATGCTTAGTGGATCTG  
TGCCTCTTACGCATATGTTACAAATTATCTGGAGTTCCTAATCAATGCAGAGTTCCCCTCCC  
CTCCGATTGTTCTAAATAATTGAAAGATGTCTGCTGTGGAAAAAGGCATGTATTTAAATCTG  
TATGATTCTCAACCATCTTTAGTTGGGAAAGGTCCTTGAAAGCCAATGGAAATACTTTTTTT  
TTTTCTTGGCACTAATCAAGTGAGTGTTACCTTTTCACTTAGTAGGATGTGTTGTTACGCTA  
GTAAAATAGAAACCTGTGTTTATTCTCAGGTATTTTAGAAACAACAGCCATCATTTTATTTT  
ATGTGTGTGTTCTTGGCTGTATTCATAAATTATATATTTTGGGCTATCAAATATTACTTCAT  
TCAATATAAATAACAATAGTAGAAGTTGTTTACTTAGATATGCTTTCTAGTTGCATTTTCTC  
AGCCTATGTAAGACTACTTTGTTGTAATAGCCTTTGAAATTTACAGTACTGTCTCTCTACTA  
TCTTCAGATTACTTGATTCAAATAAACCAATTATGTTTGTAATTGATATTAATAAAACCAGA  
ATAAAAGTTCATATCTACCC

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**FIGURE 260**

MIGYYLILFLMWGSSTVFCVLLIFTIAEASFVENECLVDLCLLRICYKLSGVPNQCRVPLP  
SDCSK



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**FIGURE 261**

GAGGATTTGCCACAGCAGCGGATAGAGCAGGAGAGCACCACCGGAGCCCTTGAGACATCCTT  
GAGAAGAGCCACAGCATAAGAGACTGCCCTGCTTGGTGT TTTTGCAGGATGATGGTGGCCCTT  
CGAGGAGCTTCTGCATTGCTGGTTCTGTTCCCTTGACGCTTTTCTGCCCCCGCCGAGTGATAC  
CCAGGACCCAGCCATGGTGCATTACATCTACCAGCGCTTTCGAGTCTTGGAGCAAGGGCTGG  
AAAAATGTACCCAAGCAACGAGGGCATAATTCAAGAATTCCAAGAGTTCTCAAAAAATATA  
TCTGTCATGCTGGGAAGATGTCAGACCTACACAAGTGAGTACAAGAGTGCAGTGGGTAACCTT  
GGCACTGAGAGTTGAACGTGCCCAACGGGAGATTGACTACATAACAATACCTTCGAGAGGCTG  
ACGAGTGCATCGTATCAGAGGACAAGACACTGGCAGAAATGTTGCTCCAAGAAGCTGAAGAA  
GAGAAAAAGATCCGGACTCTGCTGAATGCAAGCTGTGACAACATGCTGATGGGCATAAAGTC  
TTTGAATAATAGTGAAGAAGATGATGGACACACATGGCTCTTGGATGAAAGATGCTGTCTATA  
ACTCTCCAAAGGTGTACTTATTAATTGGATCCAGAAACAACACTGTTTGGGAATTTGCAAAC  
ATACGGGCATTCATGGAGGATAACACCAAGCCAGCTCCCCGGAAGCAAATCCTAACACTTTC  
CTGGCAGGGAAACAGGCCAAGTGATCTACAAAGGTTTTCTATTTTTTTCATAACCAAGCAACTT  
CTAATGAGATAATCAAATATAACCTGCAGAAGAGGACTGTGGAAGATCGAATGCTGCTCCCA  
GGAGGGGTAGGCCGAGCATTGGTTTACCAGCACTCCCCCTCAACTTACATTGACCTGGCTGT  
GGATGAGCATGGGCTCTGGGCCATCCACTCTGGGCCAGGCACCCATAGCCATTTGGTTCTCA  
CAAAGATTGAGCCGGGCACACTGGGAGTGGAGCATTGATGGGATACCCCATGCAGAAGCCAG  
GATGCTGAAGCCTCATTCTCTTGTGTGGGGTTCTCTATGTGGTCTACAGTACTGGGGGCCA  
GGGCCCTCATCGCATCACCTGCATCTATGATCCACTGGGCCTATCAGTGAGGAGGACTTGC  
CCAACCTTGTTCTTCCCCAAGAGACCAAGAAGTCACTCCATGATCCATTACAACCCAGAGAT  
AAGCAGCTCTATGCCTGGAATGAAGGAAACCAGATCATTTACAAACTCCAGACAAAGAGAAA  
GCTGCCTCTGAAGTAAATGCATTACAGCTGTGAGAAAGAGCACTGTGGCTTTGGCAGCTGTTC  
TACAGGACAGTGAGGCTATAGCCCCTTCAACAATATAGTATCCCTCTAATCACACACAGGAAG  
AGTGTGTAGAAGTGGAATAACGTATGCCTCCTTTCCCAAATGTCACTGCCTTAGGTATCTTC  
CAAGAGCTTAGATGAGAGCATATCATCAGGAAAGTTTCAACAATGTCCATTACTCCCCCAA  
CCTCCTGGCTCTCAAGGATGACCACATTCTGATACAGCCTACTTCAAGCCTTTTGT TTTTACT  
GCTCCCCAGCATTTACTGTAACCTCTGCCATCTTCCCTCCCACAATTAGAGTTGTATGCCAGC  
CCCTAATATTACCACTGGCTTTTCTCTCCCCTGGCCTTTGCTGAAGCTCTTCCCTCTTTT  
CAAATGTCTATTGATATTCTCCCATTTTCACTGCCCAACTAAAATACTATTAATATTTCTTT  
CTTTTCTTTTCTTTT TTTTGGAGACAAGGTCTCACTATGTTGCCAGGCTGGTCTCAAACCTCC  
AGAGCTCAAGAGATCCTCCTGCCTCAGCCTCCTAAGTACCTGGGATTACAGGCATGTGCCAC  
CACACCTGGCTTAAAATACTATTTCTTATTGAGGTTTAACTCTATTTCCCCTAGCCCTGTC  
CTTCCACTAAGCTTGGTAGATGTAATAATAAGTGAAAATATTAACATTTGAATATCGCTTT  
CCAGGTGTGGAGTGTTTGCACATCATTGAATTCTCGTTTCACCTTTGTGAAACATGCACAAG  
TCTTTACAGCTGTCATTCTAGAGTTTAGGTGAGTAACACAATTACAAAGTGAAAGATACAGC  
TAGAAAATACTACAAATCCCATAGTTTTTCCATTGCCCAAGGAAGCATCAAATACGTATGTT  
TGTTACCTACTCTTATAGTCAATGCGTTCATCGTTTCAGCCTAAAATAATAGTCTGTCCC  
TTTAGCCAGTTTTTCATGTCTGCACAAGACCTTTCAATAGGCCTTTCAAATGATAATTCTCTC  
AGAAAACCAGTCTAAGGGTGAGGACCCCAACTCTAGCCTCCTCTTGCTCTTGCTGTCCTCTGT  
TTCTCTCTTTCTGCTTTAAATTCAATAAAAGTGACACTGAGCAAAAAAAAAAAAAA

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**FIGURE 262**

MMVALRGASALLVLFLAAFLPPPQCTQDPAMVHYIYQRFVLEQGLEKCTQATRAYERFQE  
FSKNISVMLGRCQTYTSEYKSAVGNLALRVERAQREIDYIQYLREADECIVSEDKTLAEMLL  
QEAEKKKIRTLLNASCDNMLMGIKSLKIVKKMMDTHGSGWMKDAVYNPKVYLLIGSRNNTV  
WEFANIRAFMEDNTKPAPRKQILTLWQGTGQVIYKGFLFFHNQATSNEIIKYNLQKRTVED  
RMLLPGGVGRALVYQHSPSTYIDLAVDEHGLWAIHSGPGTHSHLVLTKEPGTLGVEHSWDT  
PCRSQDAEASFLLCGVLYVVYSTGGQGPTRITCIYDPLGTISEEDLPNLFFPKRPRSHSMIH  
YNPRDKQLYAWNEGNQIIYKLQTKRKLPLK



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**FIGURE 264**

MELSQMSELMGLSVLLGLLALMATAAVARGWLRAGEERSGRPACQKANGFPPDKSSGSKKQK  
QYQIRIRKEKPQQHNFTHRLLAAALKSHSGNISCMDFSSNGKYLATCADDRTIRIWSTKDFLQ  
REHRSMRANVELDHATLVRFSPDCRAFI VWLANGDTLRVFKMTKREDGGYTFTATPEDFPKK  
HKAPVIDIGIANTGKFIMTASSDTTVLIWSLKGQVLSTINTNQMNNTHAAVSPCGRFVASCG  
FTPDVKVWEVCFGKKGEFQEVVRAFELKGHSAAVHSFAFSNDSRRMASVSKDGTWKLWDTDV  
EYKKKQDPYLLKTGRFEEAAGAAPCRLALSPNAQVLALASGSSIHLYNTRRGEKEECFERVH  
GECIANLSFDITGRFLASCGDRAVRLFHNTPGHRAMVEEMQGHCLKRASNESTRQRLQQQLTQ  
AQETLKSLGALKK



**FIGURE 265**

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCAGG  
CAGTGTTTTGCCTTCACCCCAAGTGACCAATGAGAGGTGCCACGCGAGTCTCAATCATGCTCC  
TCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTCCAGTGT  
GGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGCACCCCGCT  
GGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTCAGGAAACGCA  
AGCACACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCGGACGGCAGGTAC  
CGCTGCTCCATGGACTTGAAGAACATCAATTTTTTAGGCGCTTGCTGGTCTCAGGATACCCA  
CCATCCTTTTCCTGAGCACAGCCTGGATTTTTTATTTCTGCCATGAAACCCAGCTCCCATGAC  
TCTCCCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGTACGCACATATGCACACAG  
GCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCTGAGGATGTCACAGCTTGAGG  
CTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGCTCAGGCTGCCAGAGAGGTGGTA  
AATGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTGACCTGCTCTCTTTCCTGGGCCCTG  
CCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAGACATTCTTGGGCACAGGCTCTTGGGT  
GCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCCTCAGGCCCTTCACGTGAGGTCTGTGAGG  
ACCAATTTGTGGGTAGTTCATCTTCCCTCGATTGGTTAACTCCTTAGTTTCAGACCACAGAC  
TCAAGATTGGCTCTTCCCAGAGGGCAGCAGACAGTCACCCCAAGGCAGGTGTAGGGAGCCCA  
GGGAGGCCAATCAGCCCCCTGAAGACTCTGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGA  
CCTGTGACCTTCTGCCAGAATTGTCATGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGT  
TAACCACTGAAGCCCCCAATTCCCACAGCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAA  
TCTAATCTGATATTGACATATTAGAAGGCAATTAGGGTGTTCCTTAAACAACCTCCTTTCCA  
AGGATCAGCCCTGAGAGCAGGTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGG  
TGGGAGCAAGGGACAGGGAGCAGGGCAGGGGCTGAAAGGGGCACTGATTCAGACCAGGGAGG  
CAACTACACACCAACATGCTGGCTTTAGAATAAAAGCACCAACTGAAAAAA

**FIGURE 266**

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAI SLWLRGLRMCTPLGREGEECHP  
GSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

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**FIGURE 267**

AGCGCCCGGGCGTCGGGGCGGTAAAAGGCCGGCAGAAGGGAGGCACTTGAGAAATGTCTTTC  
CTCCAGGACCCAAGTTTCTTCACCATGGGGATGTGGTCCATTGGTGCAGGAGCCCTGGGGGC  
TGCTGCCTTGGCATTGCTGCTTGCCAACACAGACGTGTTTCTGTCCAAGCCCCAGAAAGCGG  
CCCTGGAGTACCTGGAGGATATAGACCTGAAAACACTGGAGAAGGAACCAAGGACTTTCAA  
GCAAAGGAGCTATGGGAAAAAAATGGAGCTGTGATTATGGCCGTGCGGAGGCCAGGCTGTTT  
CCTCTGTCGAGAGGAAGCTGCGGATCTGTCCTCCCTGAAAAGCATGTTGGACCAGCTGGGCG  
TCCCCCTCTATGCAGTGGTAAAGGAGCACATCAGGACTGAAGTGAAGGATTTCCAGCCTTAT  
TTCAAAGGAGAAATCTTCCTGGATGAAAAGAAAAAGTTCTATGGTCCACAAAGGCGGAAGAT  
GATGTTTATGGGATTTATCCGTCTGGGAGTGTGGTACAACCTTCTTCCGAGCCTGGAACGGAG  
GCTTCTCTGGAAACCTGGAAGGAGAAGGCTTCATCCTTGGGGGAGTTTTTCGTGGTGGGATCA  
GGAAAGCAGGGCATTCTTCTTGAGCACCGAGAAAAAGAATTTGGAGACAAAGTAAACCTACT  
TTCTGTTCTGGAAGCTGCTAAGATGATCAAACACAGACTTTGGCCTCAGAGAAAAAATGAT  
TGTGTGAAACTGCCCAGCTCAGGGATAACCAGGGACATTCACCTGTGTTTCATGGGATGTATT  
GTTTCCACTCGTGTCCCTAAGGAGTGAGAAACCCATTTATACTCTACTCTCAGTATGGATTA  
TTAATGTATTTTAATATTCTGTTTAGGCCCACTAAGGCAAAATAGCCCCAAAACAAGACTGA  
CAAAAATCTGAAAACTAATGAGGATTATTAAGCTAAAACCTGGGAAATAGGAGGCTTAAAA  
TTGACTGCCAGGCTGGGTGCAGTGGCTCACACCTGTAATCCCAGCACTTTGGGAGGCCAAGG  
TGAGCAAGTCACTTGAGGTCGGGAGTTCGAGACCAGCCTGAGCAACATGGCGAAACCCCGTC  
TCTACTAAAAATACAAAAATCACCCGGGTGTGGTGGCAGGCACCTGTAGTCCCAGCTACCCG  
GGAGGCTGAGGCAGGAGAATCACTTGAACCTGGGAGGTGGAGGTTGCGGTGAGCTGAGATCA  
CACCACTGTATTCCAGCCTGGGTGACTGAGACTCTAACTAA

**FIGURE 268**

MSFLQDPSFFTGMWSIGAGALGAAALALLANTDVFLSKPQKALEYLEDIDLKTLEKEPR  
TFKAKELWEKNGAVIMAVRRPGCFLCREEAADLSSLKSMLDQLGVPLYAVVKEHIRTEVKDF  
QPYFKGEIFLDEKKKFYGPQRRKMMFMGFIRLGWYNFFRAWNGGFSGNLEGEFILGGVFV  
VGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK



**FIGURE 269**

ACGGACCGAGGGTTCGAGGGAGGGACACGGACCAGGAACCTGAGCTAGGTCAAAGACGCCCCG  
GGCCAGGTGCCCCGTCGCAGGTGCCCCCTGGCCGGAGATGCGGTAGGAGGGGCGAGCGCGAGA  
AGCCCCCTTCCTCGGCGCTGCCAACCCGCCACCCAGCCCATGGCGAACCCCGGGCTGGGGCTG  
CTTCTGGCGCTGGGCCTGCCGTTCTTGCTGGCCCGCTGGGGCCGAGCCTGGGGGCAAATACA  
GACCACTTCTGCAAATGAGAATAGCACTGTTTTGCCTTCATCCACCAGCTCCAGCTCCGATG  
GCAACCTGCGTCCGGAAGCCATCACTGCTATCATCGTGGTCTTCTCCCTCTTGGCTGCCTTG  
CTCCTGGCTGTGGGGCTGGCACTGTTGGTGCGGAAGCTTCGGGAGAAGCGGCAGACGGAGGG  
CACCTACCGGCCCCAGTAGCGAGGAGCAGTTCTCCCATGCAGCCGAGGCCCGGGCCCCCTCAGG  
ACTCCAAGGAGACGGTGCAGGGCTGCCTGCCCATCTAGGTCCCCCTCTCCTGCATCTGTCTCC  
CTTCATTGCTGTGTGACCTTGGGGAAAGGCAGTGCCCTCTCTGGGCAGTCAGATCCACCCAG  
TGCTTAATAGCAGGGAAGAAGGTACTTCAAAGACTCTGCCCCTGAGGTCAAGAGAGGATGGG  
GCTATTCACCTTTTATATATTTATATAAAATTAGTAGTGAGATGTAAAAAAAAAAAAAAAAAAAA

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**FIGURE 270**

MANPGLGLLLALGLPFLLARWGRAWGQIQTTSANENSTVLPSSSTSSSSDGNLRPEAITAIIV

VFSLLAALLLAVGLALLVRKLREKRQTEGTYRPSSEEQFSHAAEARAPQDSKETVQGCLPI

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**FIGURE 271**

AATATATCATCTATTTATCATTAATCAATAATGTATTCTTTTATTCCAATAACATTTGGGTT  
TTGGGATTTTAAATTTTCAAACACAGCAGAATGACATTTTTTCTGTCACTATTATTATTGTTG  
GTATGTGAAGCTATTTGGAGATCCAATTCAGGAAGCAACACATTGGAGAATGGCTACTTTCT  
ATCAAGAAATAAAGAGAACCACAGTCAACCCACACAATCATCTTTAGAAGACAGTGTGACTC  
CTACCAAAGCTGTCAAAACCACAGGCAAGGGCATAGTTAAAGGACGGAATCTTGACTCAAGA  
GGGTTAATTCTTGGTGCTGAAGCCTGGGGCAGGGGTGTAAAGAAAAACACTTAGATTCAATG  
ATTGTAAATTTAAGGCAAATACACATATTAGTATTACCTTAGTGTAATGTATCCCTGTCATA  
TATACAATAAGGTGAAATTATAAGTACCCTATGCAGTTGGCTGGACAGTTCTAAATTGGACT  
TTATTAATTTTTTAAAATCAGTAACTGATTTATCACTGGCTATGTGCTTAGATCTACAGGAGA  
TCATATAATTTGATACAAATAAAAGAAAAGTGTTCTCTCCCCTTACAGAATTGACATTTTAA  
ATGCGATACAGTTAGAATAGGAAATATGACATTAGAAAGGAAGAATGACAGGGAGAAAGGAA  
AGAAGGGAAAATGTTGCCAAGGAAAAA

**FIGURE 272**

MTFFLSLLLLLVCEAIWRSNSGSNTLENGYFLSRNKENHSQPTQSSLEDSVTPTKAVKTTGK  
GIVKGRNLDSRGLILGAEAWGRGVKKNT



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**FIGURE 273**

GCCAGGAATAACTAGAGAGGAACAATGGGGTTATTTCAGAGGTTTTGTTTTCTCTTAGTTCT  
GTGCCTGCTGCACCAGTCAAATACTTCCTTCATTAAGCTGAATAATAATGGCTTTGAAGATA  
TTGTCATTGTTATAGATCCTAGTGTGCCAGAAGATGAAAAAATAATTGAACAAATAGAGGAT  
ATGGTGACTACAGCTTCTACGTACCTGTTTGAAGCCACAGAAAAAAGATTTTTTTTCAAAAA  
TGTATCTATATTAATTCTTGAGAATTGGAAGGAAAATCCTCAGTACAAAAGGCCAAAACATG  
AAAACCATAAACATGCTGATGTTATAGTTGCACCACCTACACTCCCAGGTAGAGATGAACCA  
TACACCAAGCAGTTCACAGAATGTGGAGAGAAAGGCGAATACATTCACTTCACCCCTGACCT  
TCTACTTGGAACAAAAACAAAATGAATATGGACCACCAGGCAAACCTGTTTGTCCATGAGTGGG  
CTCACCTCCGGTGGGGAGTGTGTTGATGAGTACAATGAAGATCAGCCTTTCTACCGTGCTAAG  
TCAAAAAAATCGAAGCAACAAGGTGTTCCGCAGGTATCTCTGGTAGAAATAGAGTTTATAA  
GTGTCAAGGAGGCAGCTGTCTTAGTAGAGCATGCAGAATTGATTCTACAACAAAACCTGTATG  
GAAAAGATTGTCAATTCTTTCCTGATAAAGTACAAACAGAAAAAGCATCCATAATGTTTATG  
CAAAGTATTGATTCTGTTGTTGAATTTTGTAAACGAAAAAACCCATAATCAAGAAGCTCCAAG  
CCTACAAAACATAAAGTGCAATTTTAGAAGTACATGGGAGGTGATTAGCAATTCTGAGGATT  
TTAAAAACACCATAACCCATGGTGACACCACCTCCTCCACCTGTCTTCTCATTTGCTGAAGATC  
AGTCAAAGAATTGTGTGCTTAGTTCTTGATAAGTCTGGAAGCATGGGGGGTAAGGACCGCCT  
AAATCGAATGAATCAAGCAGCAAAACATTTCTGCTGCAGACTGTTGAAAATGGATCCTGGG  
TGGGGATGGTTCACTTTGATAGTACTGCCACTATTGTAAATAAGCTAATCCAAATAAAAAGC  
AGTGATGAAAGAAACACACTCATGGCAGGATTACCTACATATCCTCTGGGAGGAACTTCCAT  
CTGCTCTGGAATTAAATATGCATTTTCAGGTGATTGGAGAGCTACATTCCCAACTCGATGGAT  
CCGAAGTACTGCTGCTGACTGATGGGGAGGATAACACTGCAAGTTCTTGTATTGATGAAGTG  
AAACAAAGTGGGGCCATTGTTCAATTTTATTGCTTTGGGAAGAGCTGCTGATGAAGCAGTAAT  
AGAGATGAGCAAGATAACAGGAGGAAGTCATTTTTTATGTTTCAGATGAAGCTCAGAACAATG  
GCCTCATTTGATGCTTTTGGGGCTCTTACATCAGGAAATACTGATCTCTCCAGAAAGTCCCTT  
CAGCTCGAAAGTAAGGGATTAACACTGAATAGTAATGCCTGGATGAACGACACTGTCATAAT  
TGATAGTACAGTGGGAAAGGACACGTTCTTTCTCATCACATGGAACAGTCTGCCTCCAGTA  
TTTCTCTCTGGGATCCCAGTGGAAACAATAATGGAAAATTTTCACAGTGGATGCAACTTCCAAA  
ATGGCCTATCTCAGTATTCAGGAACTGCAAAGGTGGGCACTTGGGCATACAATCTTCAAGC  
CAAAGCGAACCAGAAACATTAACCTATTACAGTAACCTTCTCGAGCAGCAAATCTTCTGTGC  
CTCCAATCACAGTGAATGCTAAAATGAATAAGGACGTAAACAGTTTCCCCAGCCCAATGATT  
GTTTACGCAGAAATTCTACAAGGATATGTACCTGTTCTTGGAGCCAATGTGACTGCTTTTCAT  
TGAATCACAGAATGGACATACAGAAGTTTTGGAACCTTTTGGATAATGGTGCAGGCGCTGATT  
CTTTCAAGAATGATGGAGTCTACTCCAGGTATTTTACAGCATATACAGAAAATGGCAGATAT  
AGCTTAAAAGTTCGGGCTCATGGAGGAGCAAACACTGCCAGGCTAAAATTACGGCCTCCACT  
GAATAGAGCCGCGTACATACCAGGCTGGGTAGTGAACGGGGAAATTGAAGCAAACCCGCCAA  
GACCTGAAATTGATGAGGATACTCAGACCACCTTGGAGGATTTTCAGCCGAACAGCATCCGGA  
GGTGCATTTTGTGGTATCACAAAGTCCCAAGCCTTCCCTTGCTGACCAATACCCACCAAGTCA  
AATCACAGACCTTGATGCCACAGTTCATGAGGATAAGATTATTCTTACATGGACAGCACCAG  
GAGATAATTTTGATGTTGGAAAAGTTCAACGTTATATCATAAGAATAAGTGCAAGTATTCTT  
GATCTAAGAGACAGTTTTTGATGATGCTCTTCAAGTAAATACTACTGATCTGTCCACCAAAGGA  
GGCCAACTCCAAGGAAAGCTTTGCATTTAAACCAGAAAATATCTCAGAAGAAAATGCAACCC  
ACATATTTATTGCCATTAAAAGTATAGATAAAAGCAATTTGACATCAAAAGTATCCAACATT  
GCACAAGTAACCTTTGTTTTATCCCTCAAGCAAATCCTGATGACATTGATCCTACACCTACTCC  
TACTCCTACTCCTACTCCTGATAAAAGTCATAATTCTGGAGTTAATATTTCTACGCTGGTAT  
TGTCTGTGATTGGGTCTGTTGTAATTGTTAACTTTATTTTAAGTACCACCATTTGAACCTTA  
ACGAAGAAAAAATCTTCAAGTAGACCTAGAAGAGAGTTTTTAAAAAACAAAACAATGTAAGT  
AAAGGATATTTCTGAATCTTAAATTCATCCCATGTGTGATCATAAACTCATAAAAATAATT  
TTAAGATGTCGGAAAAGGATACTTTGATTAAATAAAAACACTCATGGATATGTAAAACTGT  
CAAGATTAAAATTTAATAGTTTCATTTATTTGTTATTTTATTTGTAAAGAAATAGTGATGAAC  
AAAGATCCTTTTTTCATACTGATACCTGGTTGTATATTATTTGATGCAACAGTTTTCTGAAAT  
GATATTTCAAATTGCATCAAGAAATTAAAATCATCTATCTGAGTAGTCAAAATACAAGTAAA  
GGAGAGCAAATAAACACATTTGGAAAAAATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AA

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**FIGURE 274**

MGLFRGFVFLVLCLLHQSNSTSF IKLNNNGFEDIVIVIDPSVPEDEKII EQIEDMVT TASTY  
LFEATEKRFFFKNVSILIPENWKENPQYKRPKHENHKHADVIVAPPTLPGRDEPYTKQFTEC  
GEKGEYIHFTPDL LLGKKQNEYGPPGKLFVHEWAHLRWGVFDEYNEDQPFYRAKSKKIEATR  
CSAGISGRNRVYKCQGGSCLSRACRIDSTTKLYGKDCQFFPDKVQTEKASIMFMQSIDSVVE  
FCNEKTHNQEAPSLQNIKCNFRSTWEVISNSED FKNTIPMVT PPPPPVFSLLKISQRIVCLV  
LDKSGSMGGKDR LNRMNQA AKHFLLQTVENG SWVGMVHFDSTATIVNKLIQIKSSDERNTLM  
AGLPTYPLGGTSICSGIKYAFQVIGELHSQLDGSEVLLLTDGEDNTASSCIDEVKQSGAIVH  
FIALGRAADEAVIEMSKITGGSHFYVSDEAQNNGLIDAFGALTSGNTDLSQKSLQLESKGLT  
LNSNAWMNDTVIIDSTVGKDTFFLITWNSLPPSISLWDPSGTIMENFTVDATSKMAYLSIPG  
TAKVGTWAYNLQAKANPETLTITVTSRAANSSVPPITVNAKMNKDVNSFPSPMIVYAEILQG  
YVPVLGANVTAFIESQNGHTEVLELLDNGAGADSFKNDGVYSRYFTAYTENGRYSLKVRAHG  
GANTARLKL RPPLNRAAYIPGWVVNGEIEANPPRPEIDEDTQTTLEDFSR TASGGAFVVSQV  
PSLPLPDQYPPSQITDL DATVHEDKI ILTWTAPGDNFDVGKVQRYIIRISASILDLRDSFDD  
ALQVNTTDLSPKEANSKESFAFKPENISEENATHIFIAIKSIDKSNLTSKVSNIAQVTLFIP  
QANPDDIDPTPTPTPTPTPKSHNSGVNISTLVLSVIGSVVIVNFILSTTI

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**FIGURE 275**

CTCCTTAGGTGGAAACCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATACGTCCCCGG  
GCAGGGGTGACAACAGGTGTCATCTTTTTTGATCTCGTGTGTGGCTGCCTTCCTATTTCAAGGAAAGAC  
GCCAAGGTAATTTTGACCCAGAGGAGCAATGATGTAGCCACCTCCTAACCTTCCCTTCTTGAACCCCC  
AGTTATGCCAGGATTTACTAGAGAGTGTCAACTCAACCAGCAAGCGGCTCCTTCGGCTTAACTTGTGG  
TTGGAGGAGAGAACCTTTGTGGGGCTGCGTTCTCTTAGCAGTGCTCAGAAGTGACTTGCCTGAGGGTG  
GACCAGAAGAAAGGAAAGGTCCCCTCTTGCTGTTGGCTGCACATCAGGAAGGCTGTGATGGGAATGAA  
GGTGAAAACCTTGGAGATTTCACTTCAGTCATTGCTTCTGCCTGCAAGATCATCCTTTAAAAGTAGAGA  
AGCTGCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAAGGAAATGGATGCAAGCAGC  
TCCGGGGGCCCCAAACGCATGCTTCCTGTGGTCTAGCCAGGGAAGCCCTTCCGTGGGGGCCCCGGCT  
TTGAGGGATGCCACCGGTTCTGGACGCATGGCTGATTCTTGAATGATGATGGTTCGCCGGGGGCTGCT  
TGCGTGGATTTCCCGGGTGGTGGTTTTGCTGGTGCTCCTCTGCTGTGCTATCTCTGTCTGTACATGT  
TGGCCTGCACCCCAAAGGTGACGAGGAGCAGCTGGCACTGCCAGGGCCAACAGCCCCACGGGGAAG  
GAGGGGTACCAGGCCGTCTTCAGGAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCG  
GCAGATCGCACAGCTCAAGGAGGAGCTGCAGGAGAGGAGTGAGCAGCTCAGGAATGGGCAGTACCAAG  
CCAGCGATGCTGCTGGCCTGGGTCTGGACAGGAGCCCCCAGAGAAAACCCAGGCCGACCTCCTGGCC  
TTCCTGCACTCGCAGGTGGACAAGGCAGAGGTGAATGCTGGCGTCAAGCTGGCCACAGAGTATGCAGC  
AGTGCCTTTCGATAGCTTTACTCTACAGAAGGTGTACCAGCTGGAGACTGGCCTTACCCGCCACCCCG  
AGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAAAGCCATTGAATCAGCCTTGGAGACC  
CTGAACAATCCTGCAGAGAACAGCCCCAATCACCGTCCTTACACGGCCTCTGATTTTCATAGAAGGGAT  
CTACCGAACAGAAAGGGACAAAGGGACATTGTATGAGCTCACCTTCAAAGGGGACCACAAACACGAAT  
TCAAACGGCTCATCTTATTTTCGACCATTTCAGCCCCATCATGAAAGTGAAAAATGAAAAGCTCAACATG  
GCCAACACGCTTATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCCGGCAGTTCATGCA  
GAATTTTCAGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGGAAAG  
AAGAAATAAATGAAGTCAAAGGAATACTTGAAAACACTTCCAAAGCTGCCAACTTCAGGAACCTTACC  
TTCATCCAGCTGAATGGAGAATTTTCTCGGGGAAAGGGACTTGATGTTGGAGCCCGCTTCTGGAAGGG  
AAGCAACGTCCTTCTCTTTTTCTGTGATGTGGACATCTACTTCACATCTGAATTCCTCAATACGTGTA  
GGCTGAATACACAGCCAGGGAAGAAGGTATTTTATCCAGTTCTTTTTCAGTCAGTACAATCCTGGCATA  
ATATACGGCCACCATGATGCAGTCCCTCCCTTGGAACAGCAGCTGGTCATAAAGAAGGAAACTGGATT  
TTGGAGAGACTTTGGATTGGGATGACGTGTCAGTATCGGTCAGACTTCATCAATATAGGTGGGTTTG  
ATCTGGACATCAAAGGCTGGGGCGGAGAGGATGTGCACCTTTATCGCAAGTATCTCCACAGCAACCTC  
ATAGTGGTACGGACGCCTGTGCGAGGACTCTTCCACCTCTGGCATGAGAAGCGCTGCATGGACGAGCT  
GACCCCCGAGCAGTACAAGATGTGCATGCAGTCCAAGGCCATGAACGAGGCATCCCACGGCCAGCTGG  
GCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTTCGCAAACAGAAACAGAAGACAAGTAGCAAA  
AAAACATGAACTCCCAGAGAAGGATTGTGGGAGACACTTTTTCTTTCTTTTGCAATTACTGAAAGTG  
GCTGCAACAGAGAAAAGACTTCCATAAAGGACGACAAAAGAATTGGACTGATGGGTCAGAGATGAGAA  
AGCCTCCGATTTCTCTCTGTTGGGCTTTTTTACAACAGAAATCAAATCTCCGCTTTGCCTGCAAAAGT  
AACCCAGTTGCACCCTGTGAAGTGTCTGACAAAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTG  
TGGAGGTTTTGATGGTGTTTACAATACTGAGACCTGTTGTTTTGTGTGCTCATTGAAATATTCATG  
ATTTAAGAGCAGTTTTGTAAAAAATTCATTAGCATGAAAGGCAAGCATATTTCTCCTCATATGAATGA  
GCCTATCAGCAGGGCTCTAGTTTCTAGGAATGCTAAAATATCAGAAGGCAGGAGAGGAGATAGGCTTA  
TTATGATACTAGTGAGTACATTAAGTAAATAAAATGGACCAGAAAAGAAAAGAAACCATAAATATCG  
TGTCATATTTTCCCCAAGATTAACCAAAAATAATCTGCTTATCTTTTTTGGTTGTCCTTTTAACTGTCT  
CCGTTTTTTTTCTTTTATTTAAAAATGCACTTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTA  
CCACTTTGCAAGCCTTACAAGAGAGCACAAGTTGGCCTACATTTTTTATATTTTTTAAGAAGATACTTT  
GAGATGCATTATGAGAACTTTCACTTCAAAGCATCAAATTGATGCCATATCCAAGGACATGCCAAATG  
CTGATTCTGTCAGGCACTGAATGTCAGGCATTGAGACATAGGGAAGGAATGGTTTGTACTAATACAGA  
CGTACAGATACTTTCTCTGAAGAGTATTTTTCGAAGAGGAGCAACTGAACACTGGAGGAAAAGAAAATG  
ACACTTTCTGCTTTACAGAAAAGGAACTCATTTCAGACTGGTGATATCGTGATGTACCTAAAAGTCAG  
AAACCACATTTTCTCCTCAGAAGTAGGGACCGCTTTCTTACCTGTTTAAATAAACCAAAGTATACCGT  
GTGAACCAAACAATCTCTTTTCAAAACAGGGTGCTCCTCCTGGCTTCTGGCTTCCATAAGAAGAAATG  
GAGAAAATATATATATATATATATATATTGTGAAAGATCAATCCATCTGCCAGAATCTAGTGGGATG  
GAAGTTTTTGCTACATGTTATCCACCCAGGCCAGGTGGAAGTAACTGAATTATTTTTTAAATTAAGC  
AGTTCTACTCAATCACCAAGATGCTTCTGAAAATTGCATTTTATTACCATTTCAAACCTATTTTTTAAA  
AATAAATACAGTTAACATAGAGTGGTTTCTTCATTTCATGTGAAAATTATTAGCCAGCACCAGATGCAT  
GAGCTAATTATCTCTTTGAGTCCTTGCTTCTGTTTGCTCACAGTAAACTCATTGTTTAAAAGCTTCAA  
GAACATTCAAGCTGTTGGTGTGTTAAAAAATGCATTGTATTGATTTGTACTGGTAGTTTATGAAATTT  
AATTAACACAGGCCATGAATGGAAGGTGGTATTGCACAGCTAATAAAATATGATTTGTGGATATGAA



**FIGURE 276**

MMVRRGLLAWISRVVLLVLLCCAISVLYMLACTPKGDEEQALALPRANSPTGKEGYQAVLQ  
EWEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADLLAFL  
HSQVDKAEVNAGVKLATEYAAVPFDSFTLQKVYQLETGLTRHPPEKPVRKDKRDELVEAIES  
ALETNNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLILFRPFSP  
MKVKNEKLNMAN TLINVIVPLAKRVDKFRQFMQNFREMCIEQDGRVHLTVVYFGKEEINEVK  
GILENTSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVDIYFTSEFLN  
LNTQPGKKVFYPVLF SQYNPGIIYGHHD AVPPLEQQLV I KKETGFWRDFGFGMTCQYRSDFI  
NIGGFDLDIKGWGGEDVHLYRKYLHSNLIVVRTPV RGLFHLWHEKRCMDELTP EQYKMCMQS  
KAMNEASHGQLGMLVFRHEIEAHLRKQKQKTSSKKT



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**FIGURE 277**

GAAAGAATGTTGTGGCTGCTCTTTTTTCTGGTGACTGCCATTCATGCTGAACTCTGTCAACC  
AGGTGCAGAAAATGCTTTTAAAGTGAGACTTAGTATCAGAACAGCTCTGGGAGATAAAGCAT  
ATGCCTGGGATACCAATGAAGAATACCTCTTCAAAGCGATGGTAGCTTTCTCCATGAGAAAA  
GTTCCCAACAGAGAAGCAACAGAAATTTCCCATGTCCTACTTTGCAATGTAACCCAGAGGGT  
ATCATTCTGGTTTGTGGTTACAGACCCTTCAAAAAATCACACCCTTCCTGCTGTTGAGGTGC  
AATCAGCCATAAGAATGAACAAGAACCGGATCAACAATGCCTTCTTTCTAAATGACCAAACCT  
CTGGAATTTTTTAAAAATCCCTTCCACACTTGCACCACCCATGGACCCATCTGTGCCCATCTG  
GATTATTATATTTGGTGTGATATTTTGCATCATCATAGTTGCAATTGCACTACTGATTTTAT  
CAGGGATCTGGCAACGTAGAAGAAAGAACAAAGAACCATCTGAAGTGGATGACGCTGAAGAT  
AAGTGTGAAAACATGATCACAATTGAAAATGGCATCCCCTCTGATCCCCTGGACATGAAGGG  
GGGCATATTAATGATGCCTTCATGACAGAGGATGAGAGGCTCACCCCTCTCTGAAGGGCTGT  
TGTTCTGCTTCCTCAAGAAATTAAACATTTGTTTCTGTGTGACTGCTGAGCATCCTGAAATA  
CCAAGAGCAGATCATATATTTTGTTTCACCATTCTTCTTTTGTAATAAATTTTGAATGTGCT  
TGAAAGTGAAAAGCAATCAATTATACCCACCAACACCACTGAAATCATAAGCTATTCACGAC  
TCAAAATATTCTAAAATATTTTTCTGACAGTATAGTGTATAAATGTGGTCATGTGGTATTTG  
TAGTTATTGATTTAAGCATTTTTTAGAAATAAGATCAGGCATATGTATATATTTTCACACTTC  
AAAGACCTAAGGAAAAATAAATTTTCCAGTGGAGAATACATATAATATGGTGTAGAAATCAT  
TGAAAATGGATCCTTTTTTGACGATCACTTATATCACTCTGTATATGACTAAGTAAACAAAAG  
TGAGAAGTAATTATTGTAAATGGATGGATAAAAATGGAATTACTCATATACAGGGTGGAATT  
TTATCCTGTTATCACACCAACAGTTGATTATATATTTTTCTGAATATCAGCCCCTAATAGGAC  
AATTCTATTTGTTGACCATTTCTACAATTTGTAAAAGTCCAATCTGTGCTAACTTAATAAAG  
TAATAATCATCTCTTTTTTAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

**FIGURE 278**

MLWLLFFLVTAIHAELCQPGAENAFKVRLSIRTALGDKAYAWDTNEEYLFKAMVAFSMRKVP  
NREATEISHVLLCNVTQRVSFVFWVTDPSKNHTLPAVEVQSAIRMNKNRINNAFFLNDQTL  
FLKIPSTLAPPMDPSVPIWIIIFGVIFCIIIVAIALLLSGIWQRRRKNKEPSEVDDAEDKC  
ENMITIENGIPSDPLDMKGGILMMP

**FIGURE 279**

AACTCAAACCTCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCAGG  
GTGTTGGAGCCCTCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTCATGT  
ATGGCAAGAGCTCTACTCGTGCGGTGCTTCTTCTCCTTGGCATAACAGCTCACAGCTCTTTGG  
CCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTGCTGGAGGCTGTTAATGGGACAGATGC  
TCGGTTAAAATGCACTTTCTCCAGCTTTGCCCTGTGGGTGATGCTCTAACAGTGACCTGGA  
ATTTTCGTCCTCTAGACGGGGGACCTGAGCAGTTTGTATTCTACTACCACATAGATCCCTTC  
CAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAATCCTGAGCGGTACGA  
TGCCTCCATCCTTCTCTGGAAACTGCAGTTCGACGACAATGGGACATACACCTGCCAGGTGA  
AGAACCCACCTGATGTTGATGGGGTGATAGGGGAGATCCGGCTCAGCGTCGTGCACACTGTA  
CGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCATTGGCTCTGCCTGTGCACTGATGATCAT  
AATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAAAAGCGATGGGCCGAAAGAGCTC  
ATAAAGTGGTGGAGATAAAATCAAAGAAGAGGAAAGGCTCAACCAAGAGAAAAAGGTCTCT  
GTTTATTTAGAAGACACAGACTTAACAATTTTAGATGGAAGCTGAGATGATTTCCAAGAACAA  
GAACCCTAGTATTTCTTGAAGTTAATGGAAACTTTTCTTTGGCTTTTCCAGTTGTGACCCGT  
TTTCCAACCAGTTCTGCAGCATATTAGATTCTAGACAAGCAACACCCCTCTGGAGCCAGCAC  
AGTGCTCCTCCATATCACCAGTCATACACAGCCTCATTATTAAGGTCTTATTTAATTTTCAGA  
GTGTAAATTTTTTCAAGTGCTCATTAGGTTTTATAACAAGAAGCTACATTTTTTGCCCTTAA  
GACACTACTTACAGTGTTATGACTTGTATACACATATATTGGTATCAAAGGGGATAAAAGCC  
AATTTGTCTGTTACATTTCTTTTACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTA  
ATGTGTTTACTCTCTTTCTTCCCACATTCTCAATTAAAAGGTGAGCTAAGCCTCCTCGGTG  
TTTCTGATTAAACAGTAAATCCTAAATTCAAACGTGTTAAATGACATTTTTTATTTTTATGTCTC  
TCCTTAACTATGAGACACATCTTGTTTTACTGAATTTCTTTCAATATTCCAGGTGATAGATT  
TTTGTCG

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**FIGURE 280**

MYGKSSTRAVLLLLLGIQLTALWPAAVEIYTSRVLEAVNGTDARLKCTFSSFAPVGDALTVT  
WNFRPLDGGPEQFVFYYHIDPFQPMSGFRKDRVSWDGNPERYDASILLWKLQFDDNGTYTCQ  
VKNPPDVDGVIGEIRLSVVHTVRFSEIHFLALALAIGSACALMIIIVIVVVLFFQHYRKKRWAER  
AHKVVEIKSKEEERLNQEKKVSVYLEDTD



**FIGURE 281**

GCATTTTGTCTGTGCTCCCTGATCTTCAGGTCACCACCATGAAGTTCTTAGCAGTCCTGGT  
ACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTCCAGCTG  
ACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCACTGCTGCT  
GCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACCACTGCTCG  
TAAAGACATTCCAGTTTTACCCAAATGGGTTGGGGATCTCCCGAATGGTAGAGTGTGTCCCT  
GAGATGGAATCAGCTTGAGTCTTCTGCAATTGGTCACAACCTATTCATGCTTCCTGTGATTTC  
ATCCAACCTACTTACCTTGCCTACGATATCCCCTTTATCTCTAATCAGTTTATTTTCTTTCAA  
ATAAAAAATAACTATGAGCAACATAAAAAAAAAAAAAA

**FIGURE 282**

MKFLAVLVLLGVSI FLVSAQNPTTAAPADTYPATGPADDEAPDAETTAAATTATTAAPTAT  
TAASTTARKDIPVLPKWVGDL PNGRVCP

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**FIGURE 283**

GGACTCTGAAGGTCCCAAGCAGCTGCTGAGGCCCCCAAGGAAGTGGTTCCAACCTTGGACCC  
CTAGGGGTCTGGATTTGCTGGTTAACAAGATAACCTGAGGGCAGGACCCCATAGGGGAATGC  
TACCTCCTGCCCTTCCACCTGCCCTGGTGTTACGGTGGCCTGGTCCCTCCTTGCCGAGAGA  
GTGTCCTGGGTCAGGGACGCAGAGGACGCTCACAGACTCCAGCCCTTTGTTACCGAGAGGAC  
ACTTGGCAAGGTCCAGCGATGGTCCGGAGTCCACACACAGACTGGCGGCAGGGCAGGAGGGG  
GACAGTTCTGTTGTGCTTGGTTGGACAGTAAGAGGGTCTTGGCCAGTCCAGGGTGGGGGGCG  
GCAAACCTCCATAAAGAACCAGAGGGTCTGGGGCCCCGGCCACAGAGTCATCTGCCCAGCTCCT  
CTGCTGCTGGCCAGTGGGAGTGGCACGAGGTGGGGCTTTGTGCCAGTTAAAACCACAGGCTGG  
ATTTGCCTGCGGGCCATGGTCCCTGTCTAGGGCAGCAATTCTCAACCTTCTTGCTCTCAGGA  
CCCCAAAGAGCTTTCATTGTATCTATTGATTTTTTACCACATTAGCAATTAAAACTGAGAAAT  
GGGCCGGGCACGGTGGCTCACGCCTGTAATCCCAGCACTTTGGGAGGCCGAGGCGGGTGGAT  
CACCTGAGATCAGGAGTTCAAGACCAGCCTGGCCAACATGGTGAAACCTTGTCTACTAAAAA  
TACAAAAAATTAGCCAGGCACAGTGGTGTGCACTGGTAGTCCCAGTTACTCGGGAGGCTGAG  
GCAGGAAAATCGCTTGAACCCAGGAGGCGGACGTTGCGGTGAGCCGAGATCGCGCCGCTGAT  
TCCAGCCTGGGCGACAAGAGTGAGACTCCATCTCACACA

**FIGURE 284**

MLPPALPPALVFTVAWSLLAERVSWVRDAEDAHRLQPFVTERTLGKVQRWSGVHTQTGGRAG  
GGQFCCAWLDSKRVLASPGWGAANSIKNQRVWAPATESSAQLLCCWPVGVARGGALCQ



**FIGURE 285**

GTCATGCCAGTGCCTGCTCTGTGCCTGCTCTGGGCCCTGGCAATGGTGACCCGGCCTGCCTCA  
GCGGCCCCCATGGGCGGCCCAGAACTGGCACAGCATGAGGAGCTGACCCTGCTCTTCCATGG  
GACCCTGCAGCTGGGCCAGGCCCTCAACGGTGTGTACAGGACCACGGAGGGACGGCTGACAA  
AGGCCAGGAACAGCCTGGGTCTCTATGGCCGCACAATAGAACTCCTGGGGCAGGAGGTCAGC  
CGGGGCCGGGATGCAGCCCAGGAACTTCGGGCAAGCCTGTTGGAGACTCAGATGGAGGAGGA  
TATTCTGCAGCTGCAGGCAGAGGCCACAGCTGAGGTGCTGGGGGAGGTGGCCCAGGCACAGA  
AGGTGCTACGGGACAGCGTGCAGCGGCTAGAAGTCCAGCTGAGGAGCGCCTGGCTGGGCCCT  
GCCTACCGAGAATTTGAGGTCTTAAAGGCTCACGCTGACAAGCAGAGCCACATCCTATGGGC  
CCTCACAGGCCACGTGCAGCGGCAGAGGCGGGAGATGGTGGCACAGCAGCATCGGCTGCGAC  
AGATCCAGGAGAGACTCCACACAGCGGCGCTCCCAGCCTTGAATCTGCCTGGATGGAAGTGA  
GACCAATCATGCTGCAAGGAACACTTCCACGCCCCGTGAGGCCCTGTGCAGGGAGGAGCTG  
CCTGTTCACTGGGATCAGCCAGGGCGCCGGGCCCCACTTCTGAGCACAGAGCAGAGACAGAC  
GCAGGCGGGGACAAAGGCAGAGGATGTAGCCCCATTGGGGAGGGGTGGAGGAAGGACATGTA  
CCCTTTCATGCCTACACACCCCTCATTAAAGCAGAGTCGTGGCATTTCAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAA

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**FIGURE 286**

MPVPALCLLWALAMVTRPASAAPMGGPELAQHEELTLLFHGTLQLGQALNGVYRTTEGRLTK  
ARNSLGLYGRTIELLGQEVSRGRDAAQELRASLLETQMEEDILQLQAEATAEVLGEVAQAQK  
VLRDSVQRLEVQLRSAWLGPAYREFEVLKAHADKQSHILWALTGHVQRQRREMVAQQHRLRQ  
IQERLHTAALPA

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**FIGURE 287**

GGCAACATGGCTCAGCAGGCTTGCCCCAGAGCCATGGCAAAGAATGGACTTGTAATTTGCAT  
CCTGGTGATCACCTTACTCCTGGACCAGACCACCAGCCACACATCCAGATTAAAAGCCAGGA  
AGCACAGCAAACGTCGAGTGAGAGACAAGGATGGAGATCTGAAGACTCAAATTGAAAAGCTC  
TGGACAGAAGTCAATGCCTTGAAGGAAATTCAAGCCCTGCAGACAGTCTGTCTCCGAGGCAC  
TAAAGTTCACAAGAAATGCTACCTTGCTTCAGAAGGTTTGAAGCATTTCCATGAGGCCAATG  
AAGACTGCATTTCCAAAGGAGGAATCCTGGTTATCCCCAGGAACTCCGACGAAATCAACGCC  
CTCCAAGACTATGGTAAAAGGAGCCTGCCAGGTGTCAATGACTTTTGGCTGGGCATCAATGA  
CATGGTCACGGAAGGCAAGTTTGTGACGTCAACGGAATCGCTATCTCCTTCCTCAACTGGG  
ACCGTGACAGCCTAACGGTGGCAAGCGAGAAAACGTGTGCCTGTTCTCCCAATCAGCTCAG  
GGCAAGTGGAGTGATGAGGCCTGTCGCAGCAGCAAGAGATACATATGCGAGTTCACCATCCC  
TAAATAGGTCTTTCTCCAATGTGTCCTCCAAGCAAGATTCATCATAACTTATAGGTTTCATGA  
TCTCTAAGATCAAGTAAAAATCATAATTTTACTTATTAAAAAATTGCAACACAAGATCAAT  
GTCCATAGCAATATGATAGCATCAGCCAATTTTGCTAACACATTTCTTTGGGATTTTGGCCCT  
TCCTGGGGTATAGGGGATCAGAAATATTGATCCATGTGCACGCAGATAAAATGGCTTCTGCT  
AAACAGACTAAAATCTTTCTCTCTAGTCTTTCTCACTTGTACAAACCCAGTTTGTTTTCAAA  
AAATCACAGTAGCAATGCAACTCATCACTCTAGAAAAGCAAGCTTAGGCTACCTGAAAGATT  
TTCCCTTGGAAGTTTAGCGTATGTTTGACTAACAAAAATTCCCTACATCAGAGACTCTAGGT  
GCTATATAATCCAAAACTTTTCAGCCTGTTGCTCATTCTGTCCCATGCTGGCAATAATACC  
TTGTCAGCCCATTACCCTTATTTTGAATTGCTCCATCTCCTGGTGGGACTTGTATCTTGTCT  
GCCATATCAGAACACAAACCCCTGAAGAGGTTCTGATTTGATTTTTTTTTTTTCTTCATGCC  
TACCCTTTTTTTTGAAGTTTCCAGCCGCAATTTGAAATGAAATGACAAGGTGTATATTTGAT  
CAATTTTCATTCCCACCATTGCATTACAACCTCTAACTTAAATGGGTAACCCTAAGGCATAT  
CAAAGAAGCAGATTGCATGATAAACGGAAATAGAAAAAAGAACCTACATTTATTTTGCTTT  
AGCATCCTTACTCTCACCTTTTATGAGATTGAGAGTGGACTTACATTTCTTTTTTACATTT  
TCGTATATTTATTTTTTTTAGCCATCATTATATGTTTAAAGTCTATTATGGGCAACCAATCTT  
TGGAAGCTGAAAACCTGAATTTAAAGAATGCTATCTTGGAATAATTGCATACGTCTGTGCAATT  
TTTTATTCTGCCTAGTGCTATTCTGCTTGTTTAACTAGATTGTACAAAATAACTTCATTGCT  
TAATATCAAATTACAAAGTTTAGACTTGGAGGGAAATGGGCTTTTTAGAGCAACAATTTT  
AAATATATTTTGTCTTCAAATAAATAGTGTTTAAACATTGAATGTGTTTTGTGAACAATAT  
CCCACTTTGCAAACCTTAACTACACATGCTTGGAATTAAGTTTTAGCTGTTTTTCATTGCTCA  
ATAATAAAGCCTGAATTCTGATCAATAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

**FIGURE 288**

MAQQACPRAMAKNGLVICILVITLLLDQTTSHTSRLKARKHSKRRVRDKDGD LKTQIEKLWT  
EVNALKEIQALQTVCLRGTKVHKKCYLASEGLKHFHEANEDCISKGGILVIPRNSDEINALQ  
DYGKRSLPGVNDFWLGINDMVTEGKFVDVNGIAISFLNWDRAQPNGGKRENCVLFSQSAQ GK  
WSDEACRSSKRYICEFTIPK



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**FIGURE 289**

GCGAGGACCGGGTATAAGAAGCCTCGTGGCCTTGCCCCGGGCAGCCGCAGGTTCCCCGCGCGC  
CCCGAGCCCCCGCGCCATGAAGCTCGCCGCCCTCCTGGGGCTCTGCGTGGCCCTGTCCTGCA  
GCTCCGCTGCTGCTTTCTTAGTGGGCTCGGCCAAGCCTGTGGCCCAGCCTGTCGCTGCGCTG  
GAGTCGGCGGCGGAGGCCGGGGCCGGGACCCTGGCCAACCCCTCGGCACCCTCAACCCGCT  
GAAGCTCCTGCTGAGCAGCCTGGGCATCCCCGTGAACCACCTCATAGAGGGCTCCCAGAAGT  
GTGTGGCTGAGCTGGGTCCCCAGGCCGTGGGGGCCGTGAAGGCCCTGAAGGCCCTGCTGGGG  
GCCCTGACAGTGTTTGGCTTGAGCCGAGACTGGAGCATCTACACCTGAGGACAAGACGCTGCC  
CACCCGCGAGGGCTGAAAACCCCGCCGCGGGGAGGACCGTCCATCCCCTTCCCCCGGCCCT  
CTCAATAAACGTGGTTAAGAGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAA

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**FIGURE 290**

MKLAALLGLCVALSCSSAAAFVGSAPVAPVALESAAEAGAGTLANPLGTLNPLKLLLS  
SLGIPVNHLEIGSQKCVNELGPQAVGAVKALKALLGALT VFG

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**FIGURE 291**

TGAAGGACTTTTCCAGGACCCAAGGCCACACACTGGAAGTCTTGCAGCTGAAGGGAGGCACT  
CCTTGGCCTCCGCAGCCGATCACATGAAGGTGGTGCCAAGTCTCCTGCTCTCCGTCCTCCTG  
GCACAGGTGTGGCTGGTACCCGGCTTGGCCCCCAGTCCTCAGTCGCCAGAGACCCAGCCCC  
TCAGAACCAGACCAGCAGGGTAGTGCAGGCTCCCAGGGAGGAAGAGGAAGATGAGCAGGAGG  
CCAGCGAGGAGAAGGCCGGTGAGGAAGAGAAAGCCTGGCTGATGGCCAGCAGGCAGCAGCTT  
GCCAAGGAGACTTCAAACCTTCGGATTTCAGCCTGCTGCGAAAGATCTCCATGAGGCACGATGG  
CAACATGGTCTTCTCTCCATTTGGCATGTCCTTGGCCATGACAGGCTTGATGCTGGGGGCCA  
CAGGGCCGACTGAAACCCAGATCAAGAGAGGGCTCCACTTGCAGGCCCTGAAGCCCACCAAG  
CCCGGGCTCCTGCCTTCCCTCTTTAAGGGACTCAGAGAGACCCTCTCCCGCAACCTGGAACCT  
GGGCCTCTCACAGGGGAGTTTTGCCTTCATCCACAAGGATTTTGATGTCAAAGAGACTTTCT  
TCAATTTATCCAAGAGGTATTTTGATACAGAGTGCCTGCTATGAATTTTCGCAATGCCTCA  
CAGGCCAAAAGGCTCATGAATCATTACATTAACAAAGAGACTCGGGGGAAAATTCCCAAACCT  
GTTTGATGAGATTAATCCTGAAACCAAATTAATTCTTGTGGATTACATCTTGTTCAAAGGGA  
AATGGTTGACCCCATTTGACCCTGTCTTCACCGAAGTCGACACTTTCCACCTGGACAAGTAC  
AAGACCATTAAGGTGCCCATGATGTACGGTGCAGGCAAGTTTGCCTCCACCTTTGACAAGAA  
TTTTCGTTGTCTATGTCCTCAAACCTGCCCTACCAAGGAAATGCCACCATGCTGGTGGTCTCA  
TGGAGAAAATGGGTGACCACCTCGCCCTTGAAGACTACCTGACCACAGACTTGGTGGAGACA  
TGGCTCAGAAACATGAAAACCAGAAACATGGAAGTTTTCTTTCCGAAGTTCAAGCTAGATCA  
GAAGTATGAGATGCATGAGCTGCTTAGGCAGATGGGAATCAGAAGAATCTTCTCACCCCTTTG  
CTGACCTTAGTGAACTCTCAGCTACTGGAAGAAATCTCCAAGTATCCAGGGTTTTACGAAGA  
ACAGTGATTGAAGTTGATGAAAGGGGCACTGAGGCAGTGGCAGGAATCTTGTGAGAAATTAC  
TGCTTATTCCATGCCTCCTGTCATCAAAGTGGACCGGCCATTTTCATTTTCATGATCTATGAAG  
AAACCTCTGGAATGCTTCTGTTTCTGGGCAGGGTGGTGAATCCGACTCTCCTATAAATTCAGG  
ACATGCATAAGCACTTCGTGCTGTAGTAGATGCTGAATCTGAGGTATCAAACACACACAGGA  
TACCAGCAATGGATGGCAGGGGAGAGTGTTCCCTTTTGTCTTAAGTATAGGGTGTCTC  
AAATAAATACAGTAGTCCCCACTTATCTGAGGGGGATACATTCAAAGACCCCCAGCAGATGC  
CTGAAACGGTGGACAGTGCTGAACCTTATATATATTTTTTCTTACACATACATACCTATGAT  
AAAGTTTAATTTATAAATTAGGCACAGTAAGAGATTAACAATAATAACAACATTAAGTAAAA  
TGAGTTACTTGAACGCAAGCACTGCAATACCATAACAGTCAAACCTGATTATAGAGAAGGCTA  
CTAAGTGACTCATGGGCGAGGAGCATAGACAGTGTGGAGACATTGGGCAAGGGGAGAATTCA  
CATCCTGGGTGGGACAGAGCAGGACGATGCAAGATTCCATCCCCTACTCAGAATGGCATGC  
TGCTTAAGACTTTTAGATTGTTTATTTCTGGAATTTTTTCATTTAATGTTTTTGGACCATGGT  
TGACCATGGTTAACTGAGACTGCAGAAAGCAAAACCATGGATAAGGGAGGACTACTACAAA  
GCATTAAATTGATACATATTTTTTAAAAA

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**FIGURE 292**

MKVVPSLLLSVLLAQVWLVPGLAPSPQSPETPAPQNQTSRVVQAPREEEDEQEASEEKAGE  
EEKAWLMASRQQLAKETS NFGFSLLRKISMRHDGNMVFS PFGMSLAMTGLMLGATGPTETQI  
KRGLHLQALKPTKPGLLPSLFKGLRETLSRNLELGLSQGSFAFIHKDFDVKETFFNLSKRYF  
DTECVPMNFRNASQAKRLMNHYINKETRGKIPKLFDEINPETKLILVDYILFKGKWLTPFDP  
VFTEVDTFHLDKYKTIKVPMMYGAGKFASTFDKNFRCHVLKLPYQGNATMLVVLMEKMGDHL  
ALEDYLTTDLVETWLRNMKTRNMEVFFPKFKLDQKYEMHELLRQMGIRRIFFSPFADLSELSA  
TGRNLQVSRVLRRTVIEVDERGTEAVAGILSEITAYSMPPVIKVDRPFHFMIYEETSGMLLF  
LGRVVNPTLL



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**FIGURE 293**

CTGGGATCAGCCACTGCAGCTCCCTGAGCACTCTCTACAGAGACGCGGACCCCAGACATGAG  
GAGGCTCCTCCTGGTCACCAGCCTGGTGGTTGTGCTGCTGTGGGAGGCAGGTGCAGTCCCAG  
CACCCAAGGTCCCTATCAAGATGCAAGTCAAACACTGGCCCTCAGAGCAGGACCCAGAGAAG  
GCCTGGGGCGCCCGTGTGGTGGAGCCTCCGGAGAAGGACGACCAGCTGGTGGTGCTGTTCCC  
TGTCCAGAAGCCGAAACTCTTGACCACCGAGGAGAAGCCACGAGGTCAGGGCAGGGGCCCA  
TCCTTCCAGGCACCAAGGCCTGGATGGAGACCGAGGACACCCTGGGCCGTGTCCTGAGTCCC  
GAGCCCGACCATGACAGCCTGTACCACCCTCCGCCTGAGGAGGACCAGGGCGAGGAGAGGCC  
CCGGTTGTGGGTGATGCCAAATCACCAGGTGCTCCTGGGACCGGAGGAAGACCAAGACCACA  
TCTACCACCCCCAGTAGGGCTCCAGGGGCCATCACTGCCCCCGCCCTGTCCCAAGGCCCAGG  
CTGTTGGGACTGGGACCCTCCCTACCCTGCCCCAGCTAGACAAATAAACCCCAGCAGGCAAA  
AAAAAAAAAAAAAAAAAAAA

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**FIGURE 294**

MRRLLLVTSLVVLLWEAGAVPAPKVPIKMQVKHWPSEQDPEKAWGARVVEPPEKDDQLVVL  
FPVQKPKLLTTEEKPRGQGRGPILPGTKAWMETEDTLGRVLSPEPDHDSLYHPPPEEDQGEE  
RPRLWVMPNHQVLLGPEEDQDHIYHPQ

**FIGURE 295**

AGAAAGCTGCACTCTGTTGAGCTCCAGGGCGCAGTGGAGGGAGGGAGTGAAGGAGCTCTCTG  
TACCCAAGGAAAGTGCAGCTGAGACTCAGACAAGATTACAATGAACCAACTCAGCTTCCTGC  
TGTTTCTCATAGCGACCACCAGAGGATGGAGTACAGATGAGGCTAATACTTACTTCAAGGAA  
TGGACCTGTTCTTCGTCTCCATCTCTGCCCAGAAGCTGCAAGGAAATCAAAGACGAATGTCC  
TAGTGCATTTGATGGCCTGTATTTTCTCCGCACTGAGAATGGTGTATCTACCAGACCTTCT  
GTGACATGACCTCTGGGGGTGGCGGCTGGACCCTGGTGGCCAGCGTG CATGAGAATGACATG  
CGTGGGAAGTGCACGGTGGGCGATCGCTGGTCCAGTCAGCAGGGCAGCAAAGCAGACTACCC  
AGAGGGGGACGGCAACTGGGCCAACTACAACACCTTTGGATCTGCAGAGGCGGCCACGAGCG  
ATGACTACAAGAACCCTGGCTACTACGACATCCAGGCCAAGGACCTGGGCATCTGGCACGTG  
CCCAATAAGTCCCCCATGCAGCACTGGAGAAACAGCTCCCTGCTGAGGTACCGCACGGACAC  
TGGCTTCCTCCAGACACTGGGACATAATCTGTTTGGCATCTACCAGAAATATCCAGTGAAAT  
ATGGAGAAGGAAAGTGTTGGACTGACAACGGCCCCGGTGATCCCTGTGGTCTATGATTTTGGC  
GACGCCCAGAAAACAGCATCTTATTACTCACCTATGGCCAGCGGGAATTC ACTGCGGGATT  
TGTT CAGTTCAGGGTATTTAATAACGAGAGAGCAGCCAACGCCTTGTGTGCTGGAATGAGGG  
TCACCGGATGTAACACTGAGCATCACTGCATTGGTGGAGGAGGATACTTTCCAGAGGCCAGT  
CCCCAGCAGTGTGGAGATTTTTCTGGTTTTGATTGGAGTGGATATGGAAC TCATGTTGGTTA  
CAGCAGCAGCCGTGAGATAACTGAGGCAGCTGTGCTTCTATTCTATCGTTGAGAGTTTTGTG  
GGAGGGAACCCAGACCTCTCCTCCCAACCATGAGATCCCAAGGATGGAGAACA ACTTACCCA  
GTAGCTAGAATGTTAATGGCAGAAGAGAAAACAATAAATCATATTGACTCAAGAAAAAAA

**FIGURE 296**

MNQLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRTEN  
GVIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRWSSQOGSKADYPEGDGNWANYNTFG  
SAEAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLLRYRTDTGFLQTLGHNLFGI  
YQKYPVKYGEKGKCTDNGPVI PVVYDFGDAQKTASYSPYGQREFTAGFVQFRVFNNERAAN  
ALCAGMRVTGCNTEHHCIGGGGYFPEASPOQCGDFSGFDWSGYGTHVGYSRSSREITEAAVLLFYR



**FIGURE 297**

GCGGAGCCGGCGCCGGCTGCGCAGAGGAGCCGCTCTCGCCGCCGCCACCTCGGCTGGGAGCC  
CACGAGGCTGCCGCATCCTGCCCTCGGAACAATGGGACTCGGCGCGCGAGGTGCTTGGGCCG  
CGCTGCTCCTGGGGACGCTGCAGGTGCTAGCGCTGCTGGGGGCCGCCCATGAAAGCGCAGCC  
ATGGCGGCATCTGCAAACATAGAGAATTCTGGGCTTCCACACAACCTCCAGTGCTAACTCAAC  
AGAGACTCTCCAACATGTGCCTTCTGACCATACAAATGAAACTTCCAACAGTACTGTGAAAC  
CACCAACTTCAGTTGCCTCAGACTCCAGTAATACAACGGTCACCACCATGAAACCTACAGCG  
GCATCTAATACAACAACACCAGGGATGGTCTCAACAAATATGACTTCTACCACCTTAAAGTC  
TACACCCAAAACAACAAGTGTTTCACAGAACACATCTCAGATATCAACATCCACAATGACCG  
TAACCCACAATAGTTCAGTGACATCTGCTGCTTCATCAGTAACAATCACAACAACCTATGCAT  
TCTGAAGCAAAGAAAGGATCAAAATTTGATACTGGGAGCTTTGTTGGTGGTATTGTATTAAC  
GCTGGGAGTTTTATCTATTCTTTACATTGGATGCAAAATGTATTACTCAAGAAGAGGCATTC  
GGTATCGAACCATAGATGAACATGATGCCATCATTTAAGGAAATCCATGGACCAAGGATGGA  
ATACAGATTGATGCTGCCCTATCAATTAATTTTGGTTTATTAATAGTTTAAAACAATATTCT  
CTTTTTGAAAATAGTATAAACAGGCCATGCATATAATGTACAGTGTATTACGTAAATATGTA  
AAGATTCTTCAAGGTAACAAGGGTTTGGGTTTTGAAATAAACATCTGGATCTTATAGACCGT  
TCATACAATGGTTTTAGCAAGTTCATAGTAAGACAAACAAGTCCTATCTTTTTTTTTTTGGCT  
GGGGTGGGGGCATTGGTCACATATGACCAGTAATTGAAAGACGTCATCACTGAAAGACAGAA  
TGCCATCTGGGCATACAAATAAGAAGTTTGTACAGCACTCAGGATTTTGGGTATCTTTTGT  
AGCTCACATAAAGAACTTCAGTGCTTTTCAGAGCTGGATATATCTTAATTACTAATGCCACA  
CAGAAATTATACAATCAAACCTAGATCTGAAGCATAATTTAAGAAAAACATCAACATTTTTTG  
TGCTTTAAACTGTAGTAGTTGGTCTAGAAACAAAATACTCC

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**FIGURE 298**

MGLGARGAWAALLLGTLLQVLALLGAAHESAAMAASANIENSGLPHNSSANSTETLQHVP  
SDH  
TNETSNSTVKPPTSVASDSSNTTVTTMKPTAASNTTTPGMVSTNMTSTTLKSTPKTTSV  
SQN  
TSQISTSTMTVTHNSSVTSAASSVTITTTMHSEAKKGSKFDTGSFVGGIVLT  
LGVLSILYIG  
CKMYYSRRGIRYRTIDEHDAII

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**FIGURE 299**

CAGCCGGGTCCCAAGCCTGTGCCTGAGCCTGAGCCTGAGCCTGAGCCCGAGCCGGGAGCCGG  
TCGCGGGGGCTCCGGGCTGTGGGACCGCTGGGCCCCCAGCGATGGCGACCCTGTGGGGAGGC  
CTTCTTCGGCTTGGCTCCTTGCTCAGCCTGTCGTGCCTGGCGCTTTCGGTGCTGCTGCTGGC  
GCAGCTGTCAGACGCCGCAAGAATTTGAGGATGTCAGATGTAAATGTATCTGCCCTCCCT  
ATAAAGAAAATTCTGGGCATATTTATAATAAGAACATATCTCAGAAAGATTGTGATTGCCTT  
CATGTTGTGGAGCCCATGCCTGTGCGGGGGCCTGATGTAGAAGCATACTGTCTACGCTGTGA  
ATGCAAATATGAAGAAAGAAGCTCTGTCACAATCAAGGTTACCATTATAATTTATCTCTCCA  
TTTTGGGCCTTCTACTTCTGTACATGGTATATCTTACTCTGGTTGAGCCCATACTGAAGAGG  
CGCCTCTTTGGACATGCACAGTTGATACAGAGTGATGATGATATTGGGGATCACCAGCCTTT  
TGCAAATGCACACGATGTGCTAGCCCGCTCCCGCAGTCGAGCCAACGTGCTGAACAAGGTAG  
AATATGCACAGCAGCGCTGGAAGCTTCAAGTCCAAGAGCAGCGAAAGTCTGTCTTTGACCGG  
CATGTTGTCCTCAGCTAATTGGGAATTGAATTCAAGGTGACTAGAAAGAAACAGGCAGACAA  
CTGGAAAGAACTGACTGGGTTTTGCTGGGTTTCATTTTAATACCTTGTTGATTTACCAACT  
GTTGCTGGAAGATTCAAACTGGAAGCAAAACTTGCTTGATTTTTTTTTCTTGTTAACGTA  
ATAATAGAGACATTTTTAAAGCACACAGCTCAAAGTCAGCCAATAAGTCTTTTCCTATTTG  
TGACTTTTACTAATAAAAATAAATCTGCCTGTAAATTATCTTGAAGTCCTTTACCTGGAACA  
AGCACTCTCTTTTTTACCACATAGTTTTAACTTGACTTTCAAGATAATTTTCAGGGTTTTTG  
TTGTTGTTGTTTTTTGTTTGTGTTGTTTGGTGGGAGAGGGGAGGGATGCCTGGGAAGTGGTT  
AACAACTTTTTTCAAGTCACTTTACTAAACAACTTTTTGTAAATAGACCTTACCTTCTATTT  
TCGAGTTTCATTTATATTTTGCAGTGTAGCCAGCCTCATCAAAGAGCTGACTTACTCATTTG  
ACTTTTGCACTGACTGTATTATCTGGGTATCTGCTGTGTCTGCACTTCATGGTAAACGGGAT  
CTAAATGCCTGGTGGCTTTTCACAAAAGCAGATTTTCTTCATGTACTGTGATGTCTGATG  
CAATGCATCCTAGAACAACTGGCCATTTGCTAGTTTACTCTAAAGACTAAACATAGTCTTG  
GTGTGTGTGGTCTTACTCATCTTCTAGTACCTTTAAGGACAAATCCTAAGGACTTGGA  
TGCAATAAAGAAATTTTATTTTAAACCAAGCCTCCCTGGATTGATAATATACACATTTG  
TCAGCATTTCCGGTCGTGGTGAGAGGCAGCTGTTTGAGCTCCAATATGTGCAGCTTTGAACT  
AGGGCTGGGGTTGTGGGTGCCTCTTCTGAAAGGTCTAACCATTATTGGATAACTGGCTTTTT  
TCTTCCTATGTCCTCTTTGGAATGTAACAATAAAAATAATTTTGAACATCAA

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**FIGURE 300**

MATLWGGLLRLGSLLSLCLALSVLLLAQLSDAAKNFEDVRCKCICPPYKENS  
GHIYNKNIS  
QKDCDCLHVVEPMPVRGPDVEAYCLRCECKYEERSSVTIKVTII IYLSILGLLLLYMVYLT  
L  
VEPILKRRLFGHAQLIQSDDDIGDHQPFANAHDVLARSRSRANVLNKVEYAQQRWK  
LQVQEQ  
RKSVFDRHVVL

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**FIGURE 301**

GCACCTGCGACCACCGTGAGCAGTCATGGCGTACTCCACAGTGCAGAGAGTCGCTCTGGCTT  
CTGGGCTTGTCCTGGCTCTGTCGCTGCTGCTGCCCAAGGCCTTCCTGTCCCGCGGGAAGCGG  
CAGGAGCCGCGCCGACACCTGAAGGAAAATTGGGCCGATTTCCACCTATGATGCATCATCA  
CCAGGCACCCTCAGATGGCCAGACTCCTGGGGCTCGTTTCCAGAGGTCTCACCTTGCCGAGG  
CATTTGCAAAGGCCAAAGGATCAGGTGGAGGTGCTGGAGGAGGAGGTAGTGGAAGAGGTCTG  
ATGGGGCAGATTATTCCAATCTACGGTTTTGGGATTTTTTTTATATATACTGTACATTCTATT  
TAAGGTAAGTAGAATCATCCTAATCATATTACATCAATGAAAATCTAATATGGCGATAAAAA  
TCATTGTCTACATTAAAACTTCTTATAGTTCATAAAATTATTTCAAATCCATCATCTCTTTA  
AATCCTGCCTCCTCTTCATGAGGTACTTAGGATAGCCATTATTTTCAGTTTCACATAAGAATG  
TTTACTCAATGTTTAAGTGTTTTGCCCCAAAATTCACAATAACAAGGCAGAACTAGGACTT  
GAACATGGATCTTTTGGTTCTTAATCCAGTGAGTGATACAATTCAATGCACTCCCCTGCCA



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**FIGURE 302**

MAYSTVQRVALASGLVLALSLLLPKAFLSRGKRQEPPTPEGKLGRFPPMMHHHQAPSDGQT  
PGARFQRSHLAFAKAKGSGGGAGGGGSGRGLMGQIIPYGFIFLYILYILFKVSRIILI  
ILHQ

**FIGURE 303**

CGGCTCGAGTGCAGCTGTGGGGAGATTTTCAGTGCATTGCCTCCCCTGGGTGCTCTTCATCTT  
GGATTTGAAAGTTGAGAGCAGCATGTTTTTGCCCACTGAAACTCATCCTGCTGCCAGTGTTAC  
TGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTCCATGTG  
GGTGATTCAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATATTCAAGAT  
AGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATACTATTACTCCA  
ATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGGGACATCTTATGC  
AATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGAACCTATATCTGTGA  
AATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTACTGCATGTGCTTCCAG  
AGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAGATGGGATGTGTTTTCCAG  
AGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTTTCAGGACGGCGCGCAAAGGA  
GGAGATTGTATTTTCGTTACTACCACAACTCAGGATGTCTGTGGAGTACTCCCAGAGCTGGG  
GCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATTTTCCGCAATGACGGTTCCATCATG  
CTTCAAGGAGTGAGGGAGTCAGATGGAGGAACTACACCTGCAGTATCCACCTAGGGAACCT  
GGTGTTCAAGAAAACCATTTGTGCTGCATGTCAGCCCGGAAGAGCCTCGAACACTGGTGACCC  
CGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGTAATCAGTTGGTGATCATTGTGGGAATTGTC  
TGTGCCACAATCCTGCTGCTCCCTGTTCTGATATTGATCGTGAAGAAGACCTGTGGAAATAA  
GAGTTCAGTGAATTCTACAGTCTTGGTGAAGAACACGAAGAAGACTAATCCAGAGATAAAAG  
AAAAACCCTGCCATTTTGAAAGATGTGAAGGGGAGAAACACATTTACTCCCCAATAATTGTA  
CGGGAGGTGATCGAGGAAGAAGAACCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCA  
CCCAGTTTGGCCTTCTCTGAGGTCAGATCGGAACAACCTCACTTGAAAAAAAGTCAGGTGGGG  
GAATGCCAAAAACACAGCAAGCCTTTTTGAGAAGAATGGAGAGTCCCTTCATCTCAGCAGCGG  
TGGAGACTCTCTCCTGTGTGTGTCCTGGGCCACTCTACCAGTGATTTTCAGACTCCCGCTCTC  
CCAGCTGTCTCCTGTCTCATTTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGG  
CAGAGAGACTGGACAGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGC  
CTCTGGAGTGGGACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCCGTT  
GGATCAGACCCTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATA  
AAAACCAACCCAAATCAA

**FIGURE 304**

MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCI FKIDWTLSPG  
EHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRLKGES  
QVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEEIVFRYY  
HKL RMSVEYSQSWG HFQNRVNLVGDI FRNDGSIMLQGVRES DGGNYTCSIHLGNLVFKKTIV  
LHVSPEEPRTLVT PAALRPLVLGGNQLV IIVGIVCATILLLPVLILIVKKT CGNKSSVNSTV  
LVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEEPSEKSEATYMTMHPVWPSLR  
SDRNNSLEKKSGGGMPKTQQAF

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**FIGURE 305**

CTATGAAGAAGCTTCCTGGAAAACAATAAGCAAAGGAAAACAAATGTGTCCCATCTCACATG  
GTTCTACCCTACTAAAGACAGGAAGATCATAACTGACAGATACTGAAATTGTAAGAGTTGG  
AAACTACATTTTGCAAAGTCATTGAACTCTGAGCTCAGTTGCAGTACTCGGGAAGCCATGCA  
GGATGAAGATGGATACATCACCTTAAATATTAAAACTCGGAAACCAGCTCTCGTCTCCGTTG  
GCCCTGCATCCTCCTCCTGGTGGCGTGTGATGGCTTTGATTCTGCTGATCCTGTGCGTGGGG  
ATGGTTGTCTGGGCTGGTGGCTCTGGGGATTTGGTCTGTGATGCAGCGCAATTACCTACAAGA  
TGAGAATGAAAATCGCACAGGAAGCTCTGCAACAATTAGCAAAGCGCTTCTGTCAATATGTGG  
TAAACAATCAGAACTAAAGGGCACTTTCAAAGGTCATAAATGCAGCCCCTGTGACACAAAC  
TGGAGATATTATGGAGATAGCTGCTATGGGTTCTTCAGGCACAACCTAACATGGGAAGAGAG  
TAAGCAGTACTGCACTGACATGAATGCTACTCTCCTGAAGATTGACAACCGGAACATTGTGG  
AGTACATCAAAGCCAGGACTCATTTAATTCGTTGGGTCGGATTATCTCGCCAGAAGTCGAAT  
GAGGTCTGGAAGTGGGAGGATGGCTCGGTTATCTCAGAAAATATGTTTGAGTTTTTGGAAGA  
TGGAAAAGGAAATATGAATTGTGCTTATTTTCATAATGGGAAAATGCACCCTACCTTCTGTG  
AGAACAACATTATTTAATGTGTGAGAGGAAGGCTGGCATGACCAAGGTGGACCAACTACCT  
TAATGC AAAGAGGTGGACAGGATAACACAGATAAGGGCTTTATTGTACAATAAAAGATATGT  
ATGAATGCATCAGTAGCTGAAAAAAAAAAAAA

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**FIGURE 306**

MQDEGGYITLNIKTRKPALVSVGPASSSWWRVMALILLILCVGMVVGLVALGIWSVMQRNYL  
QDENENRTGTLQQLAKRFCQYVVKQSELKGTFKGHKCSPCDTNWRYYGDSYGFRRHNLWE  
ESKQYCTDMNATLLKIDNRNIVEYIKARTHLIRWVGLSRQKSNEVWKWEDGSVISENMFEEFL  
EDGKGNMNCAYFHNGKMHPTECNKHLYMCERKAGMTKVDQLP



(30) 60/088,742	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,254	22 Jun/juin 1998 (22.06.1998)	US	(30) 60/091,478	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,810	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,355	23 Jun/juin 1998 (23.06.1998)	US	(30) 60/091,626	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,811	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,349	23 Jun/juin 1998 (23.06.1998)	US	(30) 60/091,628	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,824	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,429	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,633	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,825	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,431	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,646	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,826	10 Jun/juin 1998 (10.06.1998)	US	(30) 60/090,435	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,673	2 Jul/juil 1998 (02.07.1998)	US
(30) 60/088,858	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,444	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,978	7 Jul/juil 1998 (07.07.1998)	US
(30) 60/088,861	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,445	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/091,982	7 Jul/juil 1998 (07.07.1998)	US
(30) 60/088,863	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,461	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/092,182	9 Jul/juil 1998 (09.07.1998)	US
(30) 60/088,876	11 Jun/juin 1998 (11.06.1998)	US	(30) 60/090,472	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/092,472	10 Jul/juil 1998 (10.07.1998)	US
(30) 60/089,090	12 Jun/juin 1998 (12.06.1998)	US	(30) 60/090,535	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/093,339	20 Jul/juil 1998 (20.07.1998)	US
(30) 60/089,105	12 Jun/juin 1998 (12.06.1998)	US	(30) 60/090,538	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/094,651	30 Jul/juil 1998 (30.07.1998)	US
(30) 60/089,440	16 Jun/juin 1998 (16.06.1998)	US	(30) 60/090,540	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/095,282	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,512	16 Jun/juin 1998 (16.06.1998)	US	(30) 60/090,557	24 Jun/juin 1998 (24.06.1998)	US	(30) 60/095,285	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,514	16 Jun/juin 1998 (16.06.1998)	US	(30) 60/090,676	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,301	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,532	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,678	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,302	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,538	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,688	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,318	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,598	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,690	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,321	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,599	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,691	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,325	4 Aug/août 1998 (04.08.1998)	US
(30) 60/089,600	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,694	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,916	10 Aug/août 1998 (10.08.1998)	US
(30) 60/089,653	17 Jun/juin 1998 (17.06.1998)	US	(30) 60/090,695	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/095,929	10 Aug/août 1998 (10.08.1998)	US
(30) 60/089,801	18 Jun/juin 1998 (18.06.1998)	US	(30) 60/090,696	25 Jun/juin 1998 (25.06.1998)	US	(30) 60/096,012	10 Aug/août 1998 (10.08.1998)	US
(30) 60/089,907	18 Jun/juin 1998 (18.06.1998)	US	(30) 60/090,862	26 Jun/juin 1998 (26.06.1998)	US	(30) 60/096,143	11 Aug/août 1998 (11.08.1998)	US
(30) 60/089,908	18 Jun/juin 1998 (18.06.1998)	US	(30) 60/090,863	26 Jun/juin 1998 (26.06.1998)	US	(30) 60/096,146	11 Aug/août 1998 (11.08.1998)	US
(30) 60/089,947	19 Jun/juin 1998 (19.06.1998)	US	(30) 60/091,358	1 Jul/juil 1998 (01.07.1998)	US	(30) 60/096,329	12 Aug/août 1998 (12.08.1998)	US
(30) 60/089,948	19 Jun/juin 1998 (19.06.1998)	US	(30) 60/091,360	1 Jul/juil 1998 (01.07.1998)	US	(30) 60/096,757	17 Aug/août 1998 (17.08.1998)	US
(30) 60/089,952	19 Jun/juin 1998 (19.06.1998)	US	(30) 60/091,544	1 Jul/juil 1998 (01.07.1998)	US	(30) 60/096,766	17 Aug/août 1998 (17.08.1998)	US
(30) 60/090,246	22 Jun/juin 1998 (22.06.1998)	US	(30) 60/091,486	2 Jul/juil 1998 (02.07.1998)	US	(30) 60/096,768	17 Aug/août 1998 (17.08.1998)	US
(30) 60/090,252	22 Jun/juin 1998 (22.06.1998)	US	(30) 60/091,519	2 Jul/juil 1998 (02.07.1998)	US	(30) 60/096,773	17 Aug/août 1998 (17.08.1998)	US
						(30) 60/096,791	17 Aug/août 1998 (17.08.1998)	US

(30) 60/096,867	17 Aug/août 1998 (17.08.1998)	US
(30) 60/096,891	17 Aug/août 1998 (17.08.1998)	US
(30) 60/096,894	17 Aug/août 1998 (17.08.1998)	US
(30) 60/096,895	17 Aug/août 1998 (17.08.1998)	US
(30) 60/096,897	17 Aug/août 1998 (17.08.1998)	US
(30) 60/096,949	18 Aug/août 1998 (18.08.1998)	US
(30) 60/096,950	18 Aug/août 1998 (18.08.1998)	US
(30) 60/096,959	18 Aug/août 1998 (18.08.1998)	US
(30) 60/096,960	18 Aug/août 1998 (18.08.1998)	US
(30) 60/097,022	18 Aug/août 1998 (18.08.1998)	US
(30) 60/097,141	19 Aug/août 1998 (19.08.1998)	US
(30) 60/097,218	20 Aug/août 1998 (20.08.1998)	US
(30) 60/097,661	24 Aug/août 1998 (24.08.1998)	US
(30) 60/097,951	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,952	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,954	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,955	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,971	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,974	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,978	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,979	26 Aug/août 1998 (26.08.1998)	US
(30) 60/097,986	26 Aug/août 1998 (26.08.1998)	US
(30) 60/098,014	26 Aug/août 1998 (26.08.1998)	US
(30) 60/098,525	31 Aug/août 1998 (31.08.1998)	US
(30) 60/100,634	16 Sep/sep 1998 (16.09.1998)	US
(30) 60/115,565	12 Jan/jan 1999 (12.01.1999)	US